DOES NOT CIRCULATE

UNIVER OF MICH
MEDICAL LIBRARY

ACTA PHYSIOLOGICA SCANDINAVICA
VOL. 35. SUPPLEMENTUM 121.

610.5
A203

THE MESENCEPHALON AND THE VASOMOTOR SYSTEM

An Experimental Study on the Central Control of Peripheral Blood Flow in the Cat

BY

PERCY LINDGREN

STOCKHOLM 1955

UNIVERSITY OF MICHIGAN
MEDICAL LIBRARY

ACTA PHYSIOLOGICA SCANDINAVICA
VOL. 35. SUPPLEMENTUM 121.

FROM THE DEPARTMENT OF PHARMACOLOGY, KAROLINSKA INSTITUTET,
STOCKHOLM, SWEDEN

THE MESENCEPHALON AND THE VASOMOTOR SYSTEM

An Experimental Study on the Central Control of Peripheral Blood Flow in the Cat

BY

PERCY LINDGREN

STOCKHOLM 1955

Translated

by

Stanley H. Vernon

UPPSALA 1955

APPELBERGS BOKTRYCKERI AB

To the Memory of my Father

CONTENTS

Page

Preface 9

Chapter I

Introduction 10
Nervous Vasomotor Control 10
Peripheral Vasoconstrictor Nerves 11
Peripheral Vasodilator Nerves 12
Medulla Spinalis 15
Medulla Oblongata 16
Mesencephalon 19
Hypothalamus 23
Cerebral Cortex 24
Central Control of the Adrenal Medulla 26
Aim of the Present Investigation 27

Chapter II

Vascular Responses to Electric Stimulation in the Tectum and Tegmentum Mesencephali 28
Methods 29
Material 29
Anesthesia 29
Operative Preparation of the Experimental Animals 30
Neck 30
Head 30
Vascular Areas 31
Elimination of the Adrenals 32
Evisceration 32
Ligation of the Spinal Medulla 32
Decerebration 33
Technique of Cross-circulation 33
Stimulation Technique 35
Recording Technique 37
Aseptic Operations 38
Lumbar Sympathectomy 38
Denervation of Fore Paw 40
Solutions and Substances 40
Results 41
1. General Features of the Peripheral Responses 41
Comment 42

Page

2. Character and Magnitude of the Vasodilatation in the Skeletal Muscles 44
Stimulation Voltage 45
Stimulation Frequency 47
Pulse Duration 48
Duration of Stimulation 49
Comment 49

3. Character and Magnitude of Other Vascular Responses 51
Comment 52

4. Peripheral Distribution of the Vascular Responses 54
Skeletal Muscles 54
Other Vascular Areas 57
Comment 60

5. Mechanism of the Vasodilator Responses and Efferent Pathways of the Vasodilator Impulses 61
Muscle Activity—Mechanical and Metabolic Factors..... 61
Adrenaline 62
Antidromic Vasodilator Impulses in the Dorsal Roots 63
Inhibition of the Tone of Sympathetic Vasoconstrictor Nerves 63
Sympathetic Vasodilator Nerves 64
Comment 67

6. Mechanism of the Vasoconstrictor Responses and Efferent Pathways of the Vasoconstrictor Impulses 68
Comment 68

7. Peripheral Transmission of the Vasodilator Impulses 70
Effect of Atropine 70
Effect of Eserine 75
Comment 79

8. Action of a Sympatholytic Drug on the Vasodilator Responses in the Muscles and on the Vasoconstrictor Responses in the Skin 81
Comment 83

9. The Role of the Adrenals in The Vascular Reaction Pattern. 84
Responses in Muscle Vessels Deprived of their Sympathetic Innervation 85
Responses in Cutaneous Vessels Deprived of their Sympathetic Innervation 90
Effect of Adrenaline and Noradrenaline on Muscle and Cutaneous Vessels Deprived of their Sympathetic Innervation 92
Comment 98

Discussion 100

Summary and Conclusions 103

Chapter III

Page

Localization of the Stimulated Vasomotor Structures in the Mesencephalon and Adjacent Parts of the Brain 105
Methods 106
Material and Anesthesia 106
Preparation of the Animal, Stimulation and Recording Technique 106
Histologic Technique 107
Results 108
1. Histologic Examination 108
Comment 114
2. Section Experiments 115
Comment 124
Discussion 126
Summary and Conclusions 128

Chapter IV

Character of the Vasomotor Areas in the Mesencephalon and their Efferent Pathways in the Medulla Oblongata 130
Methods 131
Material 131
Anesthesia 132
Preparation of the Animal and Stimulation, Recording and Histologic Technique 132
Aseptic Operations 133
Supracollicular Decerebration 133
Infracollicular Decerebration 135
Denervation of Fore Paw 135
Results 136
1. Mesencephalon 136
Comment 140
2. Pons and Medulla Oblongata 141
Comment 146
Discussion 147
Summary and Conclusions 149

Chapter V

Some Aspects of the Functional Significance of the Mesencephalic Vasomotor Area and its Relation to Medullary Vasomotor Centers 150
Methods 151
Material and Anesthesia 151
Preparation of the Animal and Stimulation, Recording and Histologic Technique 151

Page

Results 152
1. Influence of the Mesencephalic Vasomotor Area on "Normal" Vascular Tone 152
Comment 156
2. Influence of the Baroceptor Mechanisms on the Vascular Responses to Stimulation in the Mesencephalon 158
Comment 161
3. Relation of Mesencephalofugal Vasomotor Pathways to Bulbar Vasoconstrictor and Vasodilator "Centers" 162
Comment 167
Discussion 170
Summary and Conclusions 172

CHAPTER VI

General Discussion 173

CHAPTER VII

General Summary 182

References 183

Page
152

152
156

158
161

162
167
170
172

173

182

183

PREFACE

This investigation was carried out at the Pharmacological Department, Karolinska Institutet, Stockholm, in the years 1952-1955.

I wish to express my sincere gratitude to the Head of the department, Professor Börje Uvnäs, under whose guidance I have had the privilege of working, for his interest in my work and valuable advice during every phase of it. He has generously placed the laboratory facilities of his department at my disposal.

My thanks are also due to my colleagues at the Pharmacological Department as well as other friends for their interest in my investigations and for valuable discussions.

I am especially grateful to Mrs Vesta Keiland and Miss Marianne Palmegren, who have given me skilful technical assistance, for their unsparing efforts.

The translation into English was made by Mr. Stanley H. Vernon, to whom I wish to express my appreciation.

The investigation was supported by grants from Karolinska Institutet and from Svenska Sällskapet för Medicinsk Forskning, as well as by personal grants from Karolinska Institutet (doktorandstipendium), Kungl. Vetenskapsakademien (Lindahls stipendium) and from Större Akademiska Konsistoriet, Uppsala Universitet (Lennanders stipendium). I am greatly indebted to those institutions.

Stockholm, October 1955.

Percy Lindgren

CHAPTER I.

Introduction

Nervous Vasomotor Control

Just one hundred years ago MORITZ SCHIFF (1855) demonstrated the existence of a central vasomotor control exerted by the spinal medulla via the sympathetic vasomotor nerves which had been discovered shortly before. He was able to show, too, that a higher vasomotor center was located in the medulla oblongata.

This vasomotor center in the medulla oblongata was further localized by LUDWIG and his associates and was shown to be essential for the maintenance of normal blood pressure and certain vascular reflexes (LUDWIG and THIRY, 1864; DITTMAR, 1870, 1873; OWSJANNIKOW, 1871). The observation by RANSON and BILLINGSLEY (1916) that electrical stimulation of a small circumscribed area in the rhomboid fossa produced a marked rise in blood pressure, and stimulation of an adjacent area a fall in blood pressure, prompted the more recent investigations into the central vasomotor control and into autonomic representation in the medulla oblongata.

In the past few decades, attention has also been given to supramedullary regions which have been found to be important parts of the vasomotor system. This interest has largely been focussed on the hypothalamus, and the investigations of RANSON *et al.* and HESS *et al.* concerning the importance of that part of the brain relative to autonomic functions are already classical. Similarly, cortical regions have proved to influence the cardio-vascular apparatus. As regards the mesencephalon, interest has been very slight and structures located there which belong to the vasomotor system

have been regarded merely as descending connections from the hypothalamus and cortex.

The present investigation deals with the role of the mesencephalon and, to some extent, the medulla oblongata in the central vasomotor control. In order that it may be viewed in its proper perspective, it is therefore necessary to outline some earlier results and theories. The following presentation, however, makes no claims to completeness (for a more detailed review and references to the literature, *vide* VULPIAN, 1875; BECHTEREW, 1908-11; GASKELL, 1916; BAYLISS, 1923; SPIEGEL, 1928; MÜLLER, 1931; MCDOWALL, 1938; HESS, 1948; WHITE, SMITHWICK and SIMEONE, 1952; KUNTZ, 1953).

Peripheral Vasoconstrictor Nerves

So far as is known, all vasoconstrictor nerves belong to the sympathetic nervous system. They originate from the white rami communicantes in thoracic and lumbar segments. From the sympathetic chain are distributed postganglionic vasoconstrictor fibers to various peripheral vascular areas in two ways. First, they are present in the sympathetic nerves that accompany the large arteries centrifugally, and secondly they run via the gray rami communicantes back to the spinal nerves, to join the peripheral nerves to the regions having a somatic innervation. In this way, virtually all tissues and organs receive a vasoconstrictor innervation (WOOLLARD, 1926; GILDING, 1932).

The vasoconstrictor nerves possess a certain amount of tone even under resting conditions, i.e., some impulse flow will always occur. Under such conditions this impulse flow probably amounts to 1-2 impulses per second (FOLKOW, 1952). The latter author gives an upper limit of 6-8 impulses per second under physiologic conditions, which frequency would produce almost maximal vasoconstriction. Vasoconstrictor tone is maintained by the activity of central structures—in the normal animal, chiefly via the vasoconstrictor center in the medulla oblongata.

The fact that most organs and tissues have a sympathetic vasoconstrictor innervation does not necessarily mean that the magni-

tude of the impulse flow is identical, for the vasoconstrictor tone may differ in different vascular regions. For instance, some investigators have questioned the existence of vasoconstrictor tone in skeletal muscles or have considered it to be lower than that in skin and viscera (*vide* McDowall, 1938). However, its presence in that tissue has been demonstrated conclusively (Hartman, Blatz and Kilborn, 1919; McDowall, 1950).

It is generally assumed today that the transmitter substance liberated at postganglionic vasoconstrictor nerve endings is noradrenaline. This was originally suggested by Bacq (1934). The hypothesis was strongly supported by Euler (1946 a, b), who identified noradrenaline in extracts from organs and nerves. Results that confirm this view have been reported by other investigators too (Folkow and Uvnäs, 1948 a, 1949). (For review, *vide* Euler, 1951.)

Peripheral Vasodilator Nerves

In view of the fact that the tonic vasoconstrictor innervation keeps the blood vessels in a state of contraction, it is not necessary to postulate special vasodilator nerves; for vasodilatation may conceivably be produced via inhibition of vasoconstrictor tone, in which case there will be a passive relaxation of the vessels.

Some vascular areas nevertheless possess a special vasodilator innervation. In these regions vasodilatation may accordingly be produced in two ways: by inhibition of vasoconstrictor tone and by activity in vasodilator nerves. According to the conventional anatomical and physiological view, several types of vasodilator nerves exist.

Cranial Parasympathetic Vasodilator Nerves. Some cerebral nerves possess parasympathetic vasodilator fibers, which are distributed to the tongue and glands of the oral cavity, among other regions. Probably they are not involved in more general vasomotor reflexes; for example they play no part in depressor reflexes produced by stimulation of the sinus nerve (Celander and Folkow, 1951).

Sacral Parasympathetic Vasodilator Nerves. In the ventral roots of the sacral nerves, vasodilator fibers run notably to the genitals. These vasodilator nerves have a very specialized function; probably they are only involved in local vasomotor phenomena.

Sympathetic Vasodilator Nerves. The discovery of these nerves is generally credited to DASTRE and MORAT (1880 a, b), who observed that stimulation of the cervical sympathetic produced vasodilatation in the buccal mucosa.

Since the anatomical course of the sympathetic vasodilator nerves coincides with vasoconstrictor nerves, it has naturally been difficult to study them. A serviceable technique was reported by DALE (1906, 1913) in his classical papers on ergotoxin. He showed that stimulation of the sympathetic following administration of ergotoxin produced a fall of blood pressure in the experimental animal, i.e., the opposite reaction to the rise of blood pressure before ergotoxin. DALE postulated vasodilator fibers whose effect was demonstrable when the effect of the vasoconstrictor impulses was blocked by that drug.

Many later investigations on sympathetic vasodilator nerves have been closely associated with the discussion relating to the chemical transmitter of the postganglionic vasomotor nerves. Adrenaline was long regarded as the transmitter substance at sympathetic nerve terminals. In view of the differing effects of this substance on the blood vessels in different organs, it was not unnatural to postulate it as the transmitter substance for both vasoconstrictor and vasodilator sympathetic fibers; for adrenaline in small doses was known to have a pronounced dilator action notably on muscle vessels, but in larger doses a constrictor effect (*vide* e.g. CLARK, 1930, 1934). The picture of the sympathetic vasodilator system was complicated, however, by the discovery of cholinergic sympathetic vasodilator fibers. EULER and GADDUM (1931) attributed ROGOWICZ's phenomenon to the existence of such fibers. They assumed that in a dog with denervated facial muscles, the contracture of the lips elicited by stimulation of the cervical sympathetic was due to liberation of acetylcholine at sympathetic vasodilator nerve terminals.

This theory of two different types of sympathetic vasodilator fibers prevailed until only a decade or so ago, and was dealt with, for instance, in a series of investigations conducted by BÜLBRING and BURN (BURN, 1932; BÜLBRING and BURN, 1935, 1936 a, b, c).

Together with other investigators at that time, these authors arrived at the conclusion that the occurrence of sympathetic vasodilator nerves varied from one animal species to another. Thus the dog and the hare had such nerves in profusion; the cat sparsely; but the monkey and the rabbit were devoid of them. The sympathetic vasodilator fibers, according to those authors, were distributed principally to the skeletal muscles, though also to certain areas of skin (for example, the canine ear) and to the intestinal region.

As regards the nature of the chemical transmitter substance at the nerve terminals, BÜLBRING and BURN held the view that both adrenergic and cholinergic fibers existed. The relative proportions of these two types were said to vary both in different animal species and in different tissues. Similar views were propounded by ROSENBLUETH and CANNON (1935). (These investigations were summarized in a review by BURN, 1938.)

More recent investigators, however, have questioned the existence of sympathetic vasodilator nerves with an adrenergic transmission mechanism. FOLKOW, HAEGER and UVNÄS (1948) and FOLKOW and UVNÄS (1950) thus reported observations which showed, in their opinion, that the sympathetic vasodilator nerves in the cat were solely cholinergic. In other investigations the distribution of these nerves has been studied (FOLKOW and UVNÄS, 1948 b; FOLKOW, FROST, HAEGER and UVNÄS, 1949). It has been shown, both in the cat and the dog, that they are distributed only to skeletal muscles and not to the skin and splanchnic region. GERNANDT and ZOTTERMAN (1946), who used an electrophysiologic method, also questioned the existence of vasodilator fibers in the splanchnic nerves. Experimental investigations and different views on sympathetic vasodilator nerves have been reported and discussed in detail in reviews by BURN (1938) and UVNÄS (1954).

Evidence of sympathetic vasodilator nerves to the skeletal muscles in man, too, has been presented in recent years by

BARCROFT *et al.* (BARCROFT, EDHOLM, MCMICHAEL and SHARPEY-SCHAFER, 1944; BARCROFT and EDHOLM, 1945; survey of results by BARCROFT and SWAN, 1953).

Vasodilator Fibers in Dorsal Roots. STRICKER's early observation (1876) that mechanical or electrical stimulation of a dorsal root in the lumbar region produced vasodilatation in the hind leg, prompted numerous investigations into antidromic vasodilator impulses. The copious literature includes BAYLISS's investigations conducted early this century (e.g. BAYLISS 1901, 1902; survey by BAYLISS, 1923). In his opinion, these dorsal root vasodilators played a major part in the central control of vascular tone. His results, and the views which both he and many others held regarding their functional significance, have been criticized, however. The most important question, in principle, may be whether central vasodilator impulses can be distributed via these nerves, as numerous investigators have thought (e.g. BAYLISS, 1902, 1908; FOFANOW, and TSCHALUSSOW, 1913; TOURNADE and MALMÉJAC, 1933; ROSENBLUETH and CANNON, 1934; BACH, 1946). In a detailed experimental investigation conducted by FOLKOW, STRÖM and UVNÄS (1950) this question was answered in the negative and BAYLISS's theory was strongly criticized. A similar sceptical attitude to efferent impulses in the dorsal roots has been taken by several other workers (RANSON and WIGHTMAN, 1922; BROWN and MAYCOCK, 1940; DOLE and MORISON, 1940; GRANIT and REXED, 1942; UVNÄS, 1949). Under physiologic conditions, antidromic vasodilator impulses are probably of local significance only; i.e., relative to axon reflexes.

Medulla Spinalis

It has been mentioned that the preganglionic fibers of the sympathetic vasomotor nerves run in the white rami communicantes. The cell bodies of these neurons are generally assumed to be located in the lateral horn of the gray substance of the spinal medulla. It is possible, therefore, that reflexes could be mediated via that route.

The importance of these spinal structures relative to vasomotor tone has been studied in some detail insofar as the vasoconstrictor system is concerned. Several investigators (e.g. SHERRINGTON, 1906; BOWEN, COOMBS and PIKE, 1922) have reported observations in spinal animals. Such animals fairly soon regain a normal vascular tone and normal blood pressure. Elimination, after some time, of the spinal influence, too, produces a substantial loss of tone and a fall of blood pressure. Such experiments suggest that spinal vasomotor centers possess the ability under some conditions to maintain vasoconstrictor tone.

That some vasomotor reflexes may even function without higher centers has also been demonstrated in spinal animals (SHERRINGTON, 1906; LANGLEY, 1924; BROOKS, 1933; HEYMANS, BOUCKAERT, FARBER and HSU, 1936). For instance, afferent stimulation of mixed peripheral nerves may give rise to blood pressure responses in such animals. It is known, moreover, that asphyxia produced a substantial rise of blood pressure in spinal animals (MATHISON, 1910).

As regards the significance of spinal structures relative to the sympathetic vasodilator system, nothing is known.

Even though spinal structures may under some conditions possess a certain measure of vasomotor control, these spinal centers are not considered to play any appreciable role in that respect under normal conditions, but are merely of subordinate nature. It is conceivable, however, that some reflexes may even normally be mediated by this route.

Medulla Oblongata

The medulla oblongata occupies a key position with respect to the central vasomotor control. If the nervous pathways between it and the preganglionic outflow are interrupted—for example, by section of the brain stem at the level of the obex—vasoconstrictor tone will be lost and with it there will be a substantial diminution of the peripheral resistance, manifested in greatly reduced blood pressure. On the other hand, an apparently normal

vasoconstrictor tone and blood pressure control will be retained if the communications are interrupted between the medulla oblongata and parts of the brain located higher.

The credit for having elucidated these fundamental conditions is due primarily to DITTMAR (1870, 1873) and OWSJANNIKOW (1871). By making transverse sections through the medulla oblongata at different levels and observing when a fall of blood pressure appeared, those authors localized the vasomotor center, in the rabbit and cat, to a zone at the level of the middle and rostral parts of the rhomboid fossa.

The structures responsible for this influence (on tone and reflexes) are generally designated summarily as the vasomotor center or vasoconstrictor center, as being a region dominating over the subordinate spinal centers. Different workers, on the basis of stimulation experiments, localized this center to the reticular formation between the middle and posterior thirds of the rhomboid fossa (dog) (BRUSTEIN, 1901); to the superficial structures at the inferior fovea (cat) (RANSON and BILLINGSLEY, 1916; SCOTT and ROBERTS, 1924; SCOTT, 1925); or to a somewhat larger zone in the reticular formation at the level of the inferior fovea (cat and dog) (SUH, WANG and LIM, 1936; CHEN, LIM, WANG and YI, 1936, 1937 a, b). The responsive zones were bilateral.

Several workers, using topical stimulation with e.g. the Horsley-Clarke technique, have explored and charted the whole of the medulla oblongata in cat and dog with respect to blood pressure changes (MONNIER, 1938 b, 1939; WANG and RANSON, 1939 a; ALEXANDER, 1946; BACH, 1952; MCQUEEN, BROWNE and WALKER, 1954). A study of their charts of structures that have produced pressor or depressor responses when stimulated, conveys the impression that such effects may be elicited from most parts of the medulla oblongata. It is consistently found, however, that the majority of, and the most pronounced, rises of blood pressure were obtained from the lateral portion of the reticular formation, whereas blood pressure falls were mostly elicited from the caudal part of the medial reticular formation. Naturally it is difficult with such a technique alone to decide in what degree observed effects are due to activation of afferent or efferent pathways or of cell structures.

The discovery that electrical stimulation in the distal part of the rhomboid fossa, just lateral to the obex, elicited substantial blood pressure falls (RANSON and BILLINGSLEY, 1916), gave rise to speculations about the possible existence there of a vasodilator center. This center was thought to control the activity of the various vasodilator nerves and to possess a function analogous to that of the vasoconstrictor center. These two centers were assumed to have reciprocal actions, so that pressor reflexes, for example, involved an increase of vasoconstrictor tone and a coincident decrease of vasodilator tone, whereas different depressor reflexes implied a decrease of vasoconstrictor tone and increase of vasodilator tone, the latter effected via all vasodilator nerves that were then known. This dual theory has been subscribed to by many investigators, including BAYLISS (*vide* e.g. his monograph of 1923). However, the experimental results on which his view was partly based have been criticized by several later authors. It was mentioned in the foregoing, for instance, that vasodilator fibers in the dorsal roots are not nowadays considered to conduct central impulses; a vasodilator center cannot, therefore, be in communication with them. As regards cranial parasympathetic vasodilator nerves, it was recently shown that they are not involved in depressor reflexes from the baroceptor mechanisms (CELANDER and FOLKOW, 1951). The sympathetic cholinergic vasodilator nerves were unknown in BAYLISS's time. Observations have recently been presented which suggest that these nerves, too, have no connection with the vasodilator center and are not involved in depressor reflexes (FOLKOW and UVNÄS, 1948 b; LINDGREN and UVNÄS, 1955).

What, then, is the mechanism in depressor reflexes mediated via the medulla oblongata or in direct stimulation of the vasodilator center—since in both of these instances generalized vasodilatation is unquestionably produced? Probably this vasodilatation is brought about only by inhibition of vasoconstrictor tone, either via the medullary vasoconstrictor center or by direct inhibition at spinal synapses. This inhibition theory was already held by SCOTT (1925), who did not accept BAYLISS's theories; and it has been verified by more recent observations (LIM, WANG and YI, 1938; YI, 1938; ALEXANDER, 1946; LINDGREN and UVNÄS, 1954 a).

Whether the vasodilator region in the medulla oblongata consists of transiting afferent sinus and vagus fibers, or is a real center possessing independent neurons, does not seem to have been fully elucidated. However, it has been shown that destruction of that region blocks the depressor response to afferent stimulation of the sinus and vagus nerves (LINDGREN and UVNÄS, 1954 a), which finding demonstrates that the impulses elicited are conducted via the same. In the opinion of YI (1938), the region in question constituted a true sympatho-inhibitory center.

It seems incorrect, however, to use the designation "vasodilator center", since the activity therein does not imply activity in any known vasodilator nerves, but merely inhibition of vasoconstrictor tone. "Depressor area" appears to be a better term.

The medullary organization of cranial parasympathetic vasodilator neurons will not be discussed here.

The central representation of sympathetic vasodilator nerves has in recent years been studied by UVNÄS and his associates. With regard to the medullary portion, it may be observed that the sympathetic vasodilator pathway from more rostral regions of the brain has a position differing anatomically from the dorsal structures that have been termed vasoconstrictor center and depressor area. From a comparatively narrow longitudinal band in the ventrolateral portion of the medulla oblongata and partly adjacent to the pyramidal pathway, it was possible, by electrical stimulation, to elicit activity in sympathetic vasodilator nerves to the skeletal muscles (LINDGREN and UVNÄS, 1953 a, b).

Mesencephalon

In the cat and other higher mammals the mesencephalon consists of the tectum mesencephali, containing the corpora quadrigemina, and, ventral thereto, of the tegmentum containing a large number of pathways and nuclear structures. The ventral border is formed by the pedunculi cerebri.

The mesencephalon has one characteristic in common with the medulla oblongata: all pathways and fibers to and from more rostral regions pass through it. This makes difficult an investiga-

tion of its influence on various functions, since it is hard to decide what may be attributed to "genuine" mesencephalic neurons and what must be referred to transiting fibers.

The literature concerning the influence of the mesencephalon upon autonomic functions is somewhat sparse. One of the first to investigate the influence of the corpora quadrigemina region on the blood vessels was ECKHARD (1873). He used rabbits as experimental animals and observed the appearance of the ear arteries under varying conditions. Upon mechanical stimulation of the superior colliculus he found an immediate constriction of the ear arteries, closely followed by dilatation above the normal state. He concluded that "*in der Vierhügel der Ursprung der Gefässnerven der Ohrarterien zu suchen sei*".

DANILEWSKY (1875) found that electrical stimulation of this region might produce a rise in blood pressure. Using fine electrodes, insulated except at the tips, he investigated the blood pressure response to stimulation of different sectors of the brain in curarized dogs. He found that the superficial, dorsal parts of the corpora quadrigemina had no influence upon the blood pressure; but a rise in the latter could be elicited by stimulation of the deeper parts.

Similar results were reported by other authors from that period (*vide* e.g. FERRIER, 1879, and BECHTEREW, 1909). Other autonomic responses, including mydriasis, were often observed coincidently with the effects on the circulatory apparatus. OTT (quoted by BECHTEREW, 1909), in the course of his animal experiments concerning the thermoregulation of the organism, observed that an injury of the superior colliculus might cause increased heat dissipation as a result of vasodilatation. There was a concomitant rise in blood pressure, followed after 15 seconds by a fall.

The problem as to the representation of autonomic functions in the tectum mesencephali was taken up once more by PRUS (1899), who also used electrical stimulation. He reported that a substantial rise in blood pressure could be elicited from the superior quadrigeminal bodies, especially their anterior and central parts, and sometimes from the inferior ones too. The effect generally came very rapidly at the start of stimulation, and persisted for a time after it had ceased. PRUS made his observations in dogs.

These early investigations are naturally open to criticism and they permit only of circumspect conclusions. The main objection seems to be that the results were often presented in such form as to make criticism of details impossible. With regard, for instance, to experiments with electrical stimulation of cerebral structures, it would have been interesting to know certain data concerning the stimulation. We do not know, for example, in what measure the possibility of spread of the stimulatory effect was taken into account, and hence the extent of the cerebral areas that were activated and were responsible for the responses. As regards PRUS's results, however, it is possible that the stimulation had been fairly localized; for he reported somewhat varying results from different, though fairly contiguous, parts of the region. It may also be objected, of course, that blood pressure changes, if constituting the sole observation, are a poor criterion of vasomotor phenomena; but similar criticism may also be levelled at many recent investigations.

One of the first investigations to be made with the Horsley-Clarke technique, into the influence of different parts of the brain stem on autonomic functions was that of SACHS (1911), who used cats. He reported that blood pressure responses could be elicited from the superior and inferior colliculus as well as the posterior commissure and the substantia grisea centralis. The stimuli were stated to have been of weak or moderate intensity.

In the present century not only the medulla oblongata but especially the hypothalamus have been in the forefront of interest with regard to central autonomic representation. From the autonomic point of view the mesencephalon has chiefly been considered to contain various efferent tracts from the hypothalamus. Among recent investigations, those of the RANSON group occupy a central position. In a series of papers during the nineteen-thirties, RANSON and his associates reported the results of systematic exploration, millimeter by millimeter, of the feline brain stem by topical electrical stimulation.

Their charts showed that with regard to the mesencephalic sector, responsive points—mostly yielding rises, though also falls, of blood pressure—were scattered throughout the tegmentum and the substantia grisea centralis, with some concentration to the

fasciculus centralis tegmenti. Some points were found in the basal parts of the superior colliculus and ventral and medial to the inferior colliculus (KABAT, MAGOUN and RANSON, 1935). That these authors interpreted their results, concerning the mesencephalon, largely as activation of descending connections from the hypothalamus is evident from several later papers (MAGOUN, RANSON and HETHERINGTON, 1938; WANG and RANSON, 1939 b), although they also took into account the possibility that synapses were involved. The diffuse extension of vasomotor-active structures in the mesencephalon was confirmed by experiments in which responses to stimulation of the hypothalamus were investigated before and after various transverse incisions in the mesencephalon. It was found that the lateral portions of the tegmentum probably contained the bulk of the hypothalamofugal pathways, though some were also present in medial structures. BEATTIE *et al.*, on the other hand, considered the latter structures to be the principal localization of hypothalamofugal pathways (BEATTIE, BROW and LONG, 1930 a, b; BEATTIE, 1932).

The results reported by RANSON and his coworkers have been verified by several other investigators. MCQUEEN, BROWNE and WALKER (1954), using electrical stimulation, found both pressor and depressor points in the nucleus of the commissura posterior, substantia grisea centralis, and tegmentum. THOMPSON and BACH (1950) found that similar effects could be elicited from structures in the anterior portion of the tectum (superior colliculus) and the tegmentum. HESS (1938, 1947, 1948), too, reported that blood pressure responses could be induced from the mesencephalon.

Very few researchers in recent times have directly studied the influence of the tectum mesencephali on autonomic functions, especially vasomotor ones. ALLEN (1931) nevertheless reported positive results when stimulating in the tectum mesencephali. Weak electrical stimulation in the superior colliculus of rabbits produced a moderate rise of blood pressure and an increase of the pulse amplitude; stronger stimulation induced a further blood pressure rise.

To sum up, it may be said that the existence of vasomotor neurons has been fully demonstrated in both the tectum and the

tegmentum mesencephali, but that little is known of their character—only that activation of them may give rise to pressor or depressor responses.

Hypothalamus

Together with the medulla oblongata the diencephalon is considered to play an important role in the central control of the autonomic nervous system. Numerous authors have sought to localize, in hypothalamic structures, higher centers for a number of different autonomic functions.

Among the first to emphasize the vasomotor significance of the hypothalamus were KARPLUS and KREIDL early this century. In a series of investigations they found that electrical stimulation of the walls of the third ventricle in the anterior hypothalamus produced rises in blood pressure (KARPLUS and KREIDL, 1909, 1910, 1911, 1918, 1924, 1927 a, b, 1928; review by KARPLUS, 1937). They observed, too, that similar responses could be elicited in animals where the cerebral hemispheres had been removed so long before that degeneration of corticofugal fibers had occurred. The autonomic structures in the hypothalamus were not, therefore, transiting fibers but could be regarded as centers. Similar observations on the origin of vasomotor neurons in the anterior hypothalamus, and hence the possibility of an integrative vasomotor center in that region, were reported by MAGOUN (1938) and by ELIASSON, LINDGREN and UVNÄS (1954).

Numerous investigations of the autonomic functions of the hypothalamus have since been reported; notably those of HESS *et al.* and RANSON *et al.* (for review, *vide* HESS, 1932, 1938, 1947, 1948; RANSON and MAGOUN, 1939).

As a criterion of vasomotor reactions to electrical stimulation, each of the two last-named groups chiefly employed changes of blood pressure in animals. Worthy of note is that both pressor and depressor responses were elicitable, often from largely the same regions. Vasomotor-active points were rather diffusely scattered over a large area, and no correlation to detailed

anatomical structures was demonstrable. There was nevertheless some concentration to the anterior hypothalamus, from which the structures could be traced backwards through the lateral portions towards the tegmentum and medulla oblongata.

ELIASSON, FOLKOW, LINDGREN and UVNÄS (1951), by directly recording also the peripheral circulation in different vascular areas, discovered that electrical stimulation of the feline hypothalamus often produced considerable vasodilatation in the skeletal muscles. This was claimed to be due to activity in the cholinergic sympathetic vasodilator nerves. The findings have since been confirmed with the use of an electrophysiologic technique (FOLKOW and GERNANDT, 1952).

Thermosensitive neurons are also located in the hypothalamus (*vide* e.g. RANSON, 1940; STRÖM, 1950 b); for local heating of that region produces considerable dilatation of cutaneous blood vessels by inhibition of vasoconstrictor tone.

Aside from its special significance relative to the thermoregulation, the role of the hypothalamus in the rest of the central vasomotor control has been discussed a good deal. A current view is that the hypothalamus governs the autonomic response pattern in such complex reactions as sham rage and other emergency states. Some researchers have been inclined to identify the anterior hypothalamus with a vasomotor center, directly governing the spinal structures and having the reflex- and tone-controlling functions usually attributed to the bulbar vasomotor center; which latter was thought to consist chiefly of hypothalamofugal pathways and segmental centers for cranial nerves (MÜLLER and GLASER, 1913; GLASER, 1931). Having regard to the overwhelming evidence as to the significance of the medulla oblongata (see above), such a state of affairs seems unlikely.

Cerebral Cortex

Suppositions, and even observations, that structures in the cerebral cortex have an important bearing on autonomic functions, notably vascular reactions, date back many years (STRICKER,

1886; Bechterew and Misslawsky, 1886; Weber, 1906). The more recent investigations include one conducted by Dusser de Barenne and Kleinknecht (1924) who, using electrical stimulation, explored the cortex in dogs, cats and rabbits. They elicited rises of blood pressure from the gyrus sigmoideus and falls from the anterior portion of the gyrus suprasylvius medius. These results were largely confirmed by Hoff and Green (1936). In another investigation (Green and Hoff, 1937) those authors also studied, by observing organ volume variations as a manifestation of vascular phenomena, the peripheral circulatory changes that lay behind the blood pressure responses. They interpreted the results—increase of the limb volume and decrease of the kidney volume during excitation of the motor and premotor areas—as vasodilatation in the skeletal muscles and vasoconstriction in the viscera. With regard to the extremity volume, Lund (1943, 1945) reported similar observations in cats, suggestive of vasodilatation in skeletal muscles. A direct increase of the blood flow in an isolated area of skeletal muscle on stimulation of the lateral gyrus, immediately caudal to the sulcus cruciatus, was observed by Eliasson, Lindgren and Uvnäs (1952), who interpreted the responses as vasodilatation resulting from activation of cholinergic sympathetic vasodilator nerves.

It is accordingly evident that one important autonomic function of cortical structures may be redistribution of blood from some organs to others, via vasoconstriction in the former and vasodilatation in the latter. (This view and others have been discussed in some detail by Lund, 1947; Hoff, 1949; and Christian, 1954, among others.)

The corticofugal pathways have generally been considered to run via the hypothalamus and to interfere with vasomotor structures located there. From some cortical regions, however, vasomotor fibers run together with the pyramidal tracts and continue to function even after destruction of the entire hypothalamus. There are, accordingly, both extrapyramidal and pyramidal corticofugal vasomotor fibers (Hunsicker and Spiegel, 1934; Spiegel and Hunsicker, 1936; Green and Hartzell, 1938; Wall and Davis, 1951).

Central Control of the Adrenal Medulla

Having regard to the embryonic development of the adrenal medulla, its cells must be regarded as being analogous to the postganglionic sympathetic neurons. Moreover, the ability of the adrenals to produce hormones with effects resembling the activity in sympathetic nerves has long been known.

Via impulses in the splanchnic nerves they may be activated by direct stimulation in the medulla oblongata, mesencephalon or hypothalamus, or by reflexes mediated via those central structures. (e.g. ELLIOT, 1912; CANNON and RAPPORT, 1921; HOUSSAY and MOLINELLI, 1925; CHEN, LIM, WANG and YI, 1936, 1937 a; MAGOUN, RANSON and HETHERINGTON, 1937.)

It has been shown in recent years that both adrenaline and noradrenaline are present in the secretory products of the adrenal medulla (*vide* e.g. EULER, 1951). The relationship between these two hormones has also been determined in various types of reflex activation of the adrenal medulla (KAINDL and EULER, 1951; HOLTZ, ENGELHARDT, GREEFF and SCHÜMANN, 1952; EULER and FOLKOW, 1953). Considerable interest attaches to the report that electrical stimulation of the hypothalamus may produce a selective increase of the adrenaline outflow (BRÜCKE, KAINDL and MAYER 1952), and that stimulation at various sites in that region produces sometimes chiefly a noradrenaline outflow and sometimes an adrenaline outflow (REDGATE and GELLHORN, 1953; FOLKOW and EULER, 1954). These results are very interesting in regard to the observation that noradrenaline and adrenaline occur in different adrenomedullary cells (HILLARP and HÖKFELT, 1953).

Hypoglycemia following insulin administration elicits a selective increase of the adrenaline secretion from the adrenal medulla. DUNÉR (1953) postulated a central receptor mechanism situated in the hypothalamus.

Several reflexes or other central discharges involving the sympathetic vasomotor (vasoconstrictor) system also activate the adrenal medulla. The latter's hormones thus promote by humoral means the purely nervous effects. Yet according to a recently reported investigation, the humoral component plays, in the quan-

titative sense, only a minor role in the vascular response by comparison with the nervous component (CELANDER, 1954).

Aim of the Present Investigation

In recent years UVNÄS and his coworkers have reported several investigations into the cerebral representation of the sympathetic vasodilator system. Structures belonging to that system have been localized to the cerebral cortex, hypothalamus and medulla oblongata. In the course of the experiments it was observed that the pathway from the hypothalamus probably continued in the dorsolateral direction to tectal structures. This was interesting having regard to the current view that hypothalamofugal vasomotor pathways ran chiefly in tegmental regions. At the same time, this finding brought into the foreground observations by early researchers that even tectal regions might have some vasomotor significance.

The original aim of the present investigation was, therefore, to study the mesencephalic part of the sympathetic vasodilator outflow. Due to the complex nature of the peripheral vascular effects obtained by stimulation in this area, it was found necessary to study to what degree the vascular responses were dependent on vasoconstrictor and adrenomedullary activation. Some experiments were also conducted in order to throw light on the anatomical and functional relationship of the mesencephalic structures to the medullary vasomotor center.

Some results concerning the localization in the mesencephalon have already been reported as part of an investigation, together with ROSÉN, STRANDBERG and UVNÄS (1955), into the anatomical course of the sympathetic vasodilator pathway. Other preliminary results were reported at the VIII Scandinavian Physiological Congress in Helsinki (LINDGREN, 1954).

CHAPTER II

Vascular Responses to Electric Stimulation in the Tectum and Tegmentum Mesencephali

Virtually all of the earlier investigations, outlined in the introduction, regarding the vasomotor significance of the mesencephalon have chiefly involved only observations of the experimental animals' blood pressure upon electric stimulation in the cerebral region. They have shown both rises and falls of blood pressure. No significant difference has been found in the localization of regions that have been associated with one or the other response. Positive findings at blood pressure recording may naturally be of value; they will indicate that the stimulated cerebral structure has an influence upon the vasomotor system. But they reveal nothing about the actual nature of the peripheral vascular mechanism that must lie behind these reactions; the blood pressure response is merely the resultant of them. Major variations in the peripheral resistance—vasodilatation in some vascular areas and coincident vasoconstriction in others—may also occur without being manifested in blood pressure changes. Another factor of importance to the blood pressure is, of course, the cardiac function.

In electrical stimulation in the central nervous system with the technique employed in this investigation—which has also been used by numerous other authors—it has to be borne in mind that the peripheral effects may be of very mixed character. Even though spread of the stimulation field is comparatively small in stimuli of moderate intensity, the possibility yet remains that fibers and cell groups of extremely heterogeneous character may be activated. The view that any anatomically localized area—

nucleus or tract—has a single function is tenable, according to present day theories, only in exceptional cases. Major structures often consist of a syncytium of microscopic cell groups and fibers having more or less varying functions. This is particularly true of the representation of autonomic functions in the brain stem.

It is naturally impossible, for practical reasons, to record or even to observe more than a very limited number of functions concurrently. In the present investigation the blood pressure of the experimental animals was recorded continuously. Similarly, the venous blood flow was recorded from a fairly circumscribed region of the body or, usually, from two different regions coincidently. Attention was mainly directed to a study of the increased blood flow in the skeletal muscles, elicited by electrical stimulation of mesencephalic structures, and to vascular responses simultaneously occurring in other tissues, such as skin and gut. Vascular responses which, upon stimulation, occurred without concomitant vasodilatation in the muscles were studied only to a limited degree.

Methods

Material

The material in this section of the investigation was comprised of 96 cats. (Sixteen of these underwent not only central stimulation but other measures, so that they are also included in the material in later parts of the investigation (8 of them in Chapter III:2, and 8 in Chapter V:2).) The weight varied between 1.7 and 4.8 kg, the mean being 3.0 kg. The animals' sex was not taken into account. In general no food was given for 12 hours before experiments or aseptic operations.

Anesthesia

In the majority of experiments the animals were anesthetized with Dial, 50 mg per kg (40-70 mg per kg), injected intravenously (cephalic or saphena parva). Either the vein was exposed under

initial ether anesthesia and a slender plastic tube inserted, or the injection was given percutaneously without initial anesthesia.

In the experiments conducted upon acutely decerebrated animals, only ether anesthesia was given. It was discontinued immediately after the decerebration.

Operative Preparation of the Experimental Animals

Neck. After anesthetization of the animal, the trachea was dissected free by a longitudinal incision in the ventral surface of the neck. A Y-shaped tracheal cannula of glass was inserted for the purpose of maintaining patency of the respiratory passages and of facilitating artificial respiration if required.

The common carotid artery and the vagus were dissected free on either side of the trachea and a segment of each, about 2-3 cm long, was exposed.

In some experiments the carotid sinus region too was exposed. Satisfactory visualization was obtained after resection of parts of the sternocleidomastoid and digastric muscles and of the large lymph node covering that area. After very little further dissection the sinus nerve could be directly visualized throughout its course from the carotid sinus to its junction with the glossopharyngeal nerve.

In several experiments it was desirable to avoid possible vasomotor changes due to the baroceptor mechanisms. Functional elimination of the receptors in the aortic region was effected by bilateral vagotomy, and of those in the carotid sinus either by section of the sinus nerves or bilateral occlusion of the common carotid arteries.

Animals with unsatisfactory respiration received artificial respiration by machine (pulsating positive pressure).

Head. After a longitudinal incision in the skin the temporal muscles were dissected free from their origin on the skull. With the use of a dentist's drill a hole of a square centimeter or two was made in the skull over the posterior part of the cerebral hemispheres. Any bleeding from the bone was arrested with bone wax.

In order to minimize the traumatization attending insertion of the electrodes, small incisions were made in the dura. In the few cases in which major bleeding occurred, the blood loss was substituted with dextran.

In some experiments the skin incision was prolonged in the caudal direction, and the muscles covering the occipital bone and atlanto-occipital membrane were removed. After drilling and removal of the overlying bone, the caudal portion of the cerebellum was removed so as to facilitate introduction of the electrode.

Vascular Areas. The venous blood flow in various tissues—skeletal muscles, skin and intestine—was observed.

The muscle blood flow was studied in one of the extremities, usually a hind leg. In order to eliminate the blood flow from other types of tissues (notably the skin), the leg was skinned from the inguinal region to the ankle following a longitudinal incision on the inside of the limb. Immediately above the ankle a tight ligature was applied which completely isolated the paw from the circulation. To obviate cooling, the detached skin was wrapped round the isolated muscles and sutured. A segment of the femoral vein was dissected free a few centimeters proximal to the junction with the saphena magna, to facilitate the insertion of a cannula. In those cases where intra-arterial injections were given, they were administered through a small cannula inserted into the central stump of the ligated and cut deep femoral artery. In recording of the muscle blood flow from a foreleg, in the bracheal vein, the procedure was similar.

The only vascular areas in the cat where cutaneous tissue predominates and that are suitable for the recording technique employed here—measuring of the venous outflow—are the paws. For studying the blood flow in a hind paw, a skin incision was made and the saphena magna vein dissected free for cannulization a few centimeters proximal to the ankle. To prevent a great part of the blood flow from passing, via collaterals, to the area drained by the saphena parva vein, the latter was ligated. The blood flow from a front paw was recorded in the cephalic vein, similarly cannulated a centimeter or so proximal to the ankle.

The blood flow from an intestinal area—a segment of the jejunum or the proximal part of the ileum—was recorded in an arcade vein. Following a midline incision 4-5 cm long in the abdominal wall, a vein of appropriate size was carefully dissected free without exposing any segment of the gut outside the abdominal cavity. Contiguous arcade veins were ligated so as to block any collateral pathways. After insertion of the cannula for recording, the greater part of the abdominal incision was sutured.

Elimination of the Adrenals. In studying the effects of nervous activity on the blood vessels, it is often useful to eliminate the factor consisting in the adrenomedullary activity. In many experiments this was accordingly done, either by denervation alone or, usually, by ligation of afferent and efferent blood vessels and nerves, and in some cases removal of the organ. As a rule a retroperitoneal operative technique was employed, the adrenals being reached via an incision in the flank immediately below the ribs. In a few experiments the operation was performed transperitoneally after evisceration.

Evisceration. In some experiments the animals were eviscerated. Following ligation of the large vessels to the small intestine and colon, those organs were removed; both stomach and liver, with their arterial blood supply, and the kidneys were left intact.

Ligation of the Spinal Medulla. In some experiments in which the muscle blood flow from the hind legs was studied, it was desirable to eliminate both somato-efferent and somato-afferent communications. This can be done by cutting the spinal medulla at the level of L_5, which operation interrupts the somatic innervation to that area but leaves the sympathetic intact, since the preganglionic fibers originate from segments cranial thereto. From the sympathetic chain are distributed the postganglionic fibers to the periphery via the gray rami communicantes to the spinal nerves (REIGHARD and JENNINGS, 1935; GEOHEGAN, WOLF, AIDAR, HARE and HINSEY, 1942). The only existing communication between the central nervous system and the hind legs accordingly runs via the sympathetic chain.

The operation was performed in the following manner. After the skin had been incised and the adjacent dorsal muscles removed,

one or two vertebral arches at the level of the fifth lumbar segment were drilled through with a dentist's burr. Without opening the dura, a ligature was applied round the spinal medulla. Although this method produces compression of the spinal medulla for a few millimeters on either side of the ligature, it has the advantage of not causing any appreciable bleeding. The wound was closed by a few sutures in the skin.

Decerebration. In order to obviate any influence of anesthetics on the vascular responses that were studied, a few experiments were conducted on acutely decerebrated animals. Under ether anesthesia, parts of the dome of the skull were removed by the method described above. A long longitudinal incision was made in the dura on either side of the middle line. The central parts of the hemispheres as well as the brain stem anterior to the mesencephalon were removed by suction through a glass tube (caliber 4-5 mm); in some cases the anterior portion of the mesencephalon was damaged too. At this stage the administration of ether was discontinued. In order to reduce the blood loss, the common carotids had been occluded; moreover the whole procedure was carried out rapidly. The hemorrhages from the base of the skull and other sites were arrested by tamponade with gelfoam and cotton. The entire procedure, including anesthetization, generally took about 20 minutes. An interval of a few hours was allowed before the experiment proceeded, and as a rule the animals were by then in good condition.

Technique of Cross-Circulation

A good possibility of studying the peripheral circulation is afforded by the use of cross-circulation techniques. A technique of this kind has been described by ELIASSON, FOLKOW, LINDGREN and UVNÄS (1951), among others. A hind leg was prepared in the manner described above. With the use of several tight ligatures in the skeletal muscles at the middle of the thigh, all vascular communications to the muscular area distal thereto were interrupted; the only remaining communications were via vessels

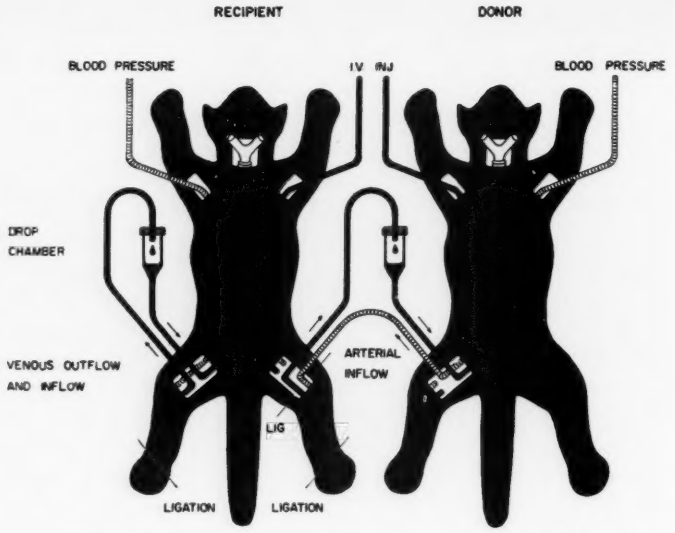


Fig. 1. Schematic representation of cross-circulation technique.

in the femur and small vessels in the ischiatic nerve, which were not ligated. However, in practice these vessels were of no importance. Outside the ligatures ran, of course, the femoral artery and vein, which had been isolated from lateral branches in a long segment from the inguinal region to the origin and entrance of the saphenous vessels. The central stump of the femoral artery in another cat, the donor, was connected via a short plastic tube to the corresponding peripheral stump in the isolated hind leg of the recipient animal. At the same time the blood flow in the femoral vein of the recipient animal was conducted, via a recording unit, to the donor animal. A schematic representation is shown in figure 1. As a rule it was sought, by eliminating and activating baroceptor mechanisms, to balance the donor animal's blood pressure with that of the recipient.

Although this technique is laborious it has many advantages. For instance, the blood flow in the cross-circulated segment cannot be mechanically influenced by blood pressure variations in the recipient animal. The perfusion pressure will remain

constant regardless of any changes of flow that may occur; the vascular sector constitutes such a small part of the donor animal's total vascular area that no change in its peripheral resistance will influence that animal's blood pressure. Moreover, any possible humoral factors from the recipient animal cannot affect the vascular changes in the perfused area. These changes must be attributed solely to activity in fibers belonging to the ischiatic nerve, for this is the only communication with the rest of the recipient animal.

Stimulation Technique

For localized electrical stimulation of subcortical brain structures the Horsley-Clarke technique is very appropriate and has been used and described by numerous investigators (e.g. HORSLEY and CLARKE, 1908; CLARKE, 1920; RANSON, 1934; HARRISON, 1938; MONNIER, 1938 a). In principle it involves fixing the animal's head in a stable metal frame, carrying one or more electrode holders that are movable in three planes at right-angles to each other. A coordinate system facilitates application of the electrode in the desired position. The electrode plane used here in mesencephalic stimulation is evident from figure 34. In stimulation of structures in the medulla oblongata and adjacent regions the electrodes were inserted in a plane diverging by about 40 degrees from the former.

The electrodes employed were of bipolar type and made of nichrome wire, 0.3 mm gauge. The wires were insulated from each other and from the environment by a coat of enamel (for details of their manufacture, *vide* RANSON, 1934). The tips of the electrodes were sharpened, to facilitate penetration into the brain substance; and only these ground surfaces were uninsulated. Two somewhat different types of electrode tip were used, as shown in figure 2. Although type A ensured the most accurate localization, it was associated with some difficulty in striking circumscribed structures, since a shift of only 1 mm or less on either side of an active point was often sufficient, in stimulation of moderate intensity, to prevent a response. Such experience

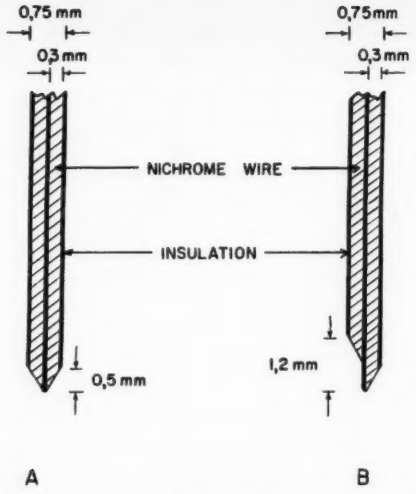


Fig. 2. Schematic representation showing the two types of electrodes used.

indicates, moreover, that with the electrodes used here the stimulated zone must be fairly small, probably 1-1.5 mm in diameter at the most. Other workers, too, have testified to the possibility of localized stimulation. RANSON (1934), for instance, writes: "*Since the electrode measures less than a millimeter in diameter and only a thin layer of enamel separates the tips of the component wires, the electrical field is small and the stimulus is restricted to a very small zone surrounding the tip. Very precise results can therefore be obtained.*"

The electrical stimulation consisted of impulses delivered by a square-wave generator. For visualizing the impulses, a cathode-ray oscillograph was connected to the generator. The latter was designed for "constant voltage" stimulation with an output resistance of 1,000 Ohms. The duration of impulses, voltage, and frequency could be varied independently of each other. Unless otherwise stated, the stimuli had a duration of 2 milliseconds and the frequency was 70 impulses per second. The output voltage was in general 1.5-3.5 volts. Each period of stimulation had a duration of 10, 15 or 20 seconds or more, governed manually or by a time relay.

The stimulator unit was designed for direct voltage too. This came into use in cases where the stimulation point was coagulated to facilitate localization (see Chapter III). In such cases the indifferent electrode was attached, for example, in the animal's tongue, and the other one consisted of the stimulating electrode.

Recording Technique

In all experiments the blood pressure was continuously recorded, either in the common carotid or the brachial or femoral artery. The artery was cannulated and, via a rubber tube filled with saline, communicated with an ordinary U-shaped mercury manometer.

The technique for recording of the venous blood flow has been described by CLEMENTZ and RYBERG (1949), HILTON (1952), HILTON and LYWOOD (1954), and LINDGREN and UVNÄS (1954 b). In principle the method consisted in directing the blood flow from a cannulated vein, via a plastic tube, to a drop chamber. A phototube drop counter operated an ordinate recorder. From the drop chamber the blood stream was returned to the animal, entering either the cannulated proximal stump of the same vein or another vein—usually, for practical reasons, the external jugular. The extracorporeal passage of the blood necessitated heparinization of the animal. This was produced with about 25 mg heparin per kg in a 5 per cent solution, given intravenously.

For a recording unit with tubes and drop chamber, the extracorporeal blood volume amounted to about 3 ml. The tubes naturally presented some resistance to the blood flow. To gain an idea of its magnitude, the resistance was determined at varying velocities of flow. The results are shown in figure 3. In the case of e.g. a minute volume below 12 ml—which value was only occasionally reached—the resistance was less than 6 cm H_2O. The method was thus associated with an increased venous pressure in the vascular area studied. However, the method was found to have no disadvantages in comparison with an open method, in which the venous outflow runs against the atmospheric pressure.

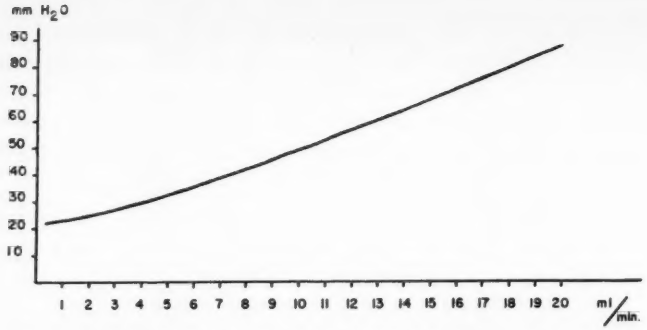


Fig. 3. Diagram showing the resistance in a blood flow recording unit (plastic tubes, inner diameter 2.0 mm, and drop chamber, inner diameter 12 mm, total length 60 cm) at different rates.

In order to minimize the heat loss from the blood during its extracorporeal passage, the plastic tube was enclosed in a larger outer tube, so that an air space was formed between the two. This notwithstanding, it was impossible to avoid some cooling of the blood, as will be seen from figure 4. However, it did not influence the animal's body temperature, which was kept constant by the heating devices of the operating table.

In most experiments the blood flow was recorded in two vascular areas concurrently; in some experiments, in one area only, and in others, in three different areas.

Aseptic Operations

Lumbar Sympathectomy. The animals were anesthetized with 25-30 mg Nembutal per kg intraperitoneally. After a midline incision through the abdominal wall the gut and urinary bladder were retracted with warm, moist packs. Lateral to the aorta the dorsal peritoneum was incised and the left sympathetic chain exposed by blunt dissection. Commencing in the cranial part at the level of L_3-L_4, all efferent and afferent pathways were then cut, after which the entire chain was removed ganglion by ganglion. In general, not more than two ganglia distal to the promon-

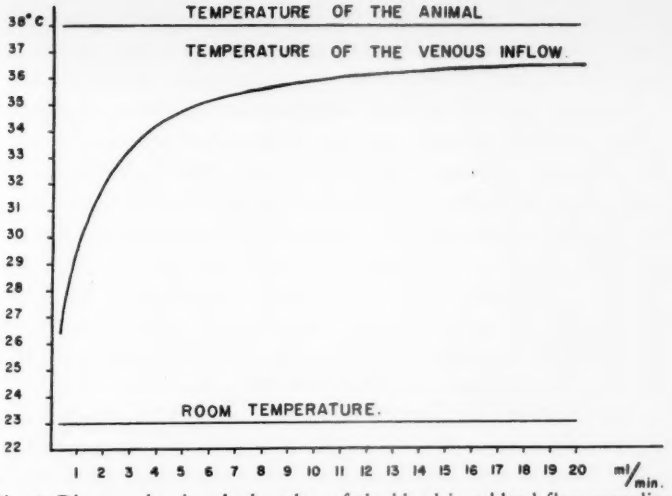


Fig. 4. Diagram showing the heat loss of the blood in a blood flow recording unit at different rates.

tory could be removed. In some cases the most caudal visible ganglion was inseparable from that on the right side; both ganglia were then removed. After careful hemostasis the dorsal peritoneum was sutured, and likewise the ventral peritoneum and abdominal muscles. The wound was then closed with continuous steel sutures. A single dose of 0.25 gm streptomycin was injected into the abdominal cavity. No further postoperative treatment was given.

The operation deprived the left hind leg of its sympathetic innervation. This latter is considered to consist partly of postganglionic fibers along the larger arteries and partly of fibers in the gray rami communicantes to the spinal nerves. The latter type of fibers, functionally the most important, are distributed with the peripheral nerves to all vascular areas (GILDING, 1932). The preganglionic communications to sympathetic fibers in the ischiatic nerve run in white rami communicantes in the fourth lumbar and segments cranial thereto. The postganglionic ones run in gray rami communicantes to spinal nerves L_6-S_1 (L_5-S_2) (REIGHARD and JENNINGS, 1935; GEOHEGAN, WOLF, AIDAR, HARE and HINSEY, 1942). The animals were used after some time for

observations of the blood flow, principally in the lower leg muscles, the innervation of which consists substantially of branches from the ischiatic nerve.

Denervation of Fore Paw. The operation was performed under ether anesthesia of short duration. After a short skin incision in the axillary fossa and blunt dissection of overlying muscles, the nerves running from the brachial plexus to the fore leg—median, radial, ulnar, etc.—could be inspected. Each of them was cut and segments 1-3 cm long removed in order to prolong and make difficult the regeneration. The wound was closed with a few steel sutures. No postoperative treatment was given. The animals often developed some flexion posture of the denervated paw after a time, and mild decubiti sometimes occurred.

This operation interrupted virtually all nervous communications to the fore leg; i.e., the sympathetic ones too.—The sympathetic fibers running along the large arteries are, as mentioned above, of no practical significance relative to the peripheral vasomotor innervation. The animals were used after some time for observations of the blood flow in the skin (paw).

Solutions and Substances

(Chapters II, III, IV and V)

Dial (Ciba), (Diallylbarbituric acid).
Nembutal (Abbot) (diluted in 20 % ethyl alcohol), (Sodium ethyl [1-methylbutyl] barbiturate, Pentobarbital Sodium).
Aether ad narcosin (Sw.Ph.XI), (Ether).
1-Epinephrine bitartrate (Winthrop-Stearns), (Adrenaline, Epinephrine).
1-Arterenol bitartrat (Leo), (Noradrenaline, Norepinephrine).
Acetylcholin "Roche" (Hoffman-La Roche), (Acetylcholine).
Atropini sulfas (Sw.Ph.XI), (Atropine).
Physostigmine salicylate P.S.XI. (Bios), (Eserine).
Dihydroergotamine (Sandoz), (Dihydroergotamine).
Heparin Vitrum (Vitrum) 5 %, (Heparin).
Macrodex (Pharmacia), (Dextran).

Spongostan (Ferrosan), (Gelfoam).
Strepsulfat (Kabi), (Streptomycin).
Suspenin (Kabi), (Penicillin).

Those of the above-mentioned drugs that are not supplied in solution and that were used for injection, were dissolved in 0.9 per cent saline unless otherwise stated. Similarly, all dilutions were made with 0.9 per cent saline. Unstable solutions were prepared immediately before each particular experiment.

Results

1. General Features of the Peripheral Responses

Numerous experiments confirmed the reports of earlier investigators regarding pressor and depressor responses to mesencephalic stimulation. The blood pressure responses varied considerably in character and magnitude from one animal to another. As a general rule, stimuli of high intensity produced a rise of blood pressure. Moreover, a depressor response could generally be changed to a pressor response by increasing the intensity. Sometimes the rises in blood pressure were biphasic, with a rapid phase and a slower and lower, though more prolonged phase. The latter component was observed especially in experiments on animals with intact adrenals.

Observations of the behavior of the blood flow in different organs upon stimulation provided, however, some explanation of the irregular pattern of the blood pressure responses; for these were often associated with substantial changes of blood flow, particularly on stimulation in tectal regions. Such changes sometimes occurred, however, even without any demonstrable blood pressure response. The explanation seems to be that increases of blood flow in an organic system—the skeletal muscles—were compensated by decreases in other parts, the cutaneous and splanchnic areas. The baroceptor mechanisms naturally played an important part, too, in equalizing the blood pressure responses. Their role is studied especially in Chapter V and, to some degree,

in section 5 of the present chapter. It may already be observed here, however, that the baroceptor mechanisms did not play any qualitative part in the peripheral responses.

In some experiments, notwithstanding systematic exploration of the mesencephalon, no increase of blood flow could be elicited in the skeletal muscles. Yet rises of blood pressure could invariably be obtained, provided the intensity of stimulation was increased sufficiently, from different parts of the mesencephalon, and particularly from tegmental structures. They were sometimes attended by a decrease in e.g. the cutaneous blood flow; more rarely was there any reduction of the muscular blood flow.

Insertion of the electrode occasionally gave rise to intracerebral bleeding of varying extent. In the case of minor hemorrhages round the electrode tip, no effects could be elicited upon repeated stimulation. In the case of larger hemorrhages, displacement and compression often prevented continuation of the experiments. Similarly, cerebral edema sometimes occurred without any manifest cause, and rendered the structures considerably less sensitive to electrical stimulation.

Other responses to stimulation—autonomic or somatic—were not systematically studied. In one or two experiments the animals' pupils were studied, and both dilatation and contraction could be detected, depending on the region stimulated. The heart rate was observed in a few cases, though without any direct recording. Either it showed no changes upon stimulation producing increase of blood flow in the skeletal muscles and only a minor effect on the blood pressure, or a slight increase of rate could be observed.

Uncoordinated motor responses sometimes occurred in response to stimulation, at times with a change in the depth of respiration, occasionally of convulsive type.

Comment

The observation that if electrical stimulation in the mesencephalon, especially tectal regions, produced a change in blood pressure, then it usually consisted of a rise, is consistent with the results of earlier investigations (e.g. Prus, 1899; Sachs, 1911; Allen, 1931). Some workers have reported, however, that depres-

sor responses may occur too (e.g. KABAT, MAGOUN and RANSON, 1935; THOMPSON and BACH, 1950). In none of the above-mentioned investigations was any attempt made to analyze the peripheral phenomena, and it may well be that stimulation points which perhaps gave major changes in the peripheral circulation were quite overlooked as vasomotor-active if no change occurred in the blood pressure.

In view of the position of the mesencephalon as an integral part of the brain stem, with its numerous pathways, it is not surprising that stimulation also affects neurons which activate other parts of the sympathetic system than vasomotor components. KNOLL's (1869) early observation (made by FERRIER, 1879, too) that electrical stimulation of the superior colliculus may produce dilatation of the pupil, was verified. As regards the representation of other sympathetic functions in this region of the brain, an observation by LANGWORTHY and RICHTER (1930) is also worthy of note; for they were able to activate sweat glands in the paws of cats by stimulation in the basal part of the superior colliculus. Activation of pilomotor nerves by electrical stimulation immediately ventral to the superior and inferior colliculi has also been reported (BROWN and SHERRINGTON, 1911).

Many experiments were conducted with the vagus nerves cut, among other things for the purpose of eliminating effects on the heart; but even animals with intact vagi seldom presented bradycardia, as was reported for instance by PRUS (1899).

Some authors (*vide* e.g. ALLEN, 1931) have reported a change in respiration on stimulation in the region of the superior colliculus. Several animals in the present investigation received artificial respiration, so that any effects which stimulation may have had on the respiration were not observed there. Having regard, for instance, to the similar results in animals with their respiration intact and in those artificially respirated, the respiratory effects which sometimes occurred are not likely, however, to have influenced the responses appreciably.

Most of the experiments were, as pointed out above, performed under Dial anesthesia. As regards autonomic functions, it is known that electrical stimulation in some part of the brain may produce a fall of blood pressure or a minor rise under Dial anesthesia, but a

distinct rise under e.g. ether anesthesia. The phenomenon was described, for instance, by GREEN and HOFF (1937) in cortical stimulation in cats and monkeys. LANGFORD, BERNHAUT and HOFF (1954) reported a comparative study in dogs, with similar results, in the case of pentobarbital and ether anesthesia respectively. The phenomenon in question is not likely to have any qualitative significance—as will be seen in sections 4, 5 and 6 mesencephalic stimulation activated both vasodilator and vasoconstrictor fibers —though it should be borne in mind in quantitative evaluation of the observations made. (With regard to Dial as an anesthetic in neurologic experiments, excitability, etc., *vide* also FULTON, LIDDELL and RIOCH, 1930.)

The use of a barbiturate as anesthetic in studying the effects of activity in cholinergic nerves may seem debatable in view of the atropine-like peripheral action of the barbiturate group. BURN (1938), in his monograph on sympathetic vasodilator fibers, pointed out that barbiturates may have other effects on the experimental animal besides the purely anesthetic action. It may chiefly be N-methylated barbiturates [Evipan (Bayer) and the like], however, that possess atropinelike characteristics (EMMELIN, 1941). In such respects Dial was not observed to have any drawbacks. Similar sympathetic responses to those in the present investigation were studied, in stimulation in the medulla oblongata, by LINDGREN and UVNÄS (1953 b), using different anesthetics (Dial and chloralose), but no qualitative differences were detected. For the purpose of investigating further the influence of the anesthetic, control experiments were performed on acutely decerebrated animals (section 7), i.e., without any anesthesia whatsoever. They showed the same results as those in animals anesthetized with Dial.

2. Character and Magnitude of the Vasodilatation in the Skeletal Muscles

Electrical stimulation in the tectum opticum, 3-5 mm below the surface of the superior colliculus, 2-6 mm from the middle line, usually resulted in an increase of the blood flow through the

skeletal muscles, often without any appreciable change in blood pressure. Typical effects are shown, for example, in figure 5. A latent period of 4-7 seconds after the start of stimulation was followed by an abrupt increase of blood flow, usually amounting to 100-300 per cent.

The maximal magnitude and duration of this increase in flow varied with different parameters of stimuli, such as intensity, frequency and so on. Major variations from one animal to another were observed too. As a general rule, the higher the initial vascular tone the greater, relatively speaking, was the increase of flow with the same parameters of stimuli.

Characteristic of those increases of blood flow which were shown to be due to vasodilatation in the skeletal muscles was the effect that atropine had upon them. Atropinization with 0.1-0.2 mg per kg completely blocked them and smaller doses reduced them. In the present investigation this behavior was taken as a criterion that the vasodilatations elicited in different experiments were of the same character and effected by the same mechanism. For vasodilatation may be produced in skeletal muscles, as is known, by mechanisms not affected by atropine. An example of these is the inhibition of vasoconstrictor tone by electrical stimulation in the depressor area of the medulla oblongata (LINDGREN and UVNÄS, 1954 a) or by stimulation of a sinus nerve (LINDGREN and UVNÄS, 1955). Similarly, vasodilatation produced in skeletal muscles by adrenaline is not influenced by atropine. (The effect of atropine on the responses elicited is discussed further in section 7.)

Stimulation Voltage

In the majority of experiments the amplitude of the stimuli was equivalent to 1.5 to 3.5 volts. An increase of blood flow produced by stimuli of this intensity usually amounted to 100-300 per cent. It is somewhat difficult, however, quantitatively to compare stimulation data with the recorded responses in different experimental animals. A better idea of the magnitude of increases in blood flow can be obtained by comparing them, in one and the same experiment, with other increases produced e.g. by intra-

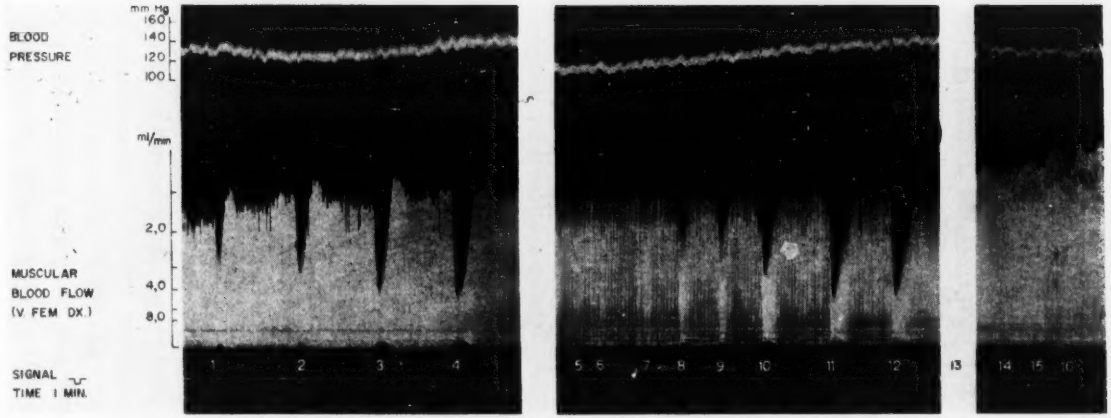


Fig. 5. Cat 2.0 kg. Dial 50 mg/kg. A. carotis commun. sin. occluded.

Vasodilator responses in the muscles of the right hind leg to intra-arterial injections of various doses of acetylcholine and to stimulation of varying intensity in the right part of the tectum mesencephali.[1 2]

1.	0.001 μg acetylcholine I.A.	Increase of flow	50 %	9.	Stimulation, 1.5 V, 10 sec.	Increase of flow	60 %
2.	0.01 „ „ — „ „	„ „ „	110 %	10.	„ — „ 2.5 „ „ „	„ „ „	140 %
3.	0.1 „ „ — „ „	„ „ „	180 %	11.	„ — „ 3.5 „ „ „	„ „ „	260 %
4.	1 „ „ — „ „	„ „ „	230 %	12.	„ — „ 5.0 „ „ „	„ „ „	230 %
5.	Stimulation, 0.25 V, 10 sec.	„ „ „	—	13.	Atropine 0.2 mg/kg I.V.		
6.	„ — „ 0.50 „ „ „	„ „ „	—	14.	Stimulation, 1.5 V, 10 sec.	„ „ „	—
7.	„ — „ 0.75 „ „ „	„ „ „	< 20 %	15.	„ — „ 2.5 „ „ „	„ „ „	—
8.	„ — „ 1.0 „ „ „	„ „ „	60 %	16.	„ — „ 3.5 „ „ „	„ „ „	< 20 %

Note the absence of blood pressure reactions.

arterial injections of acetylcholine. An experiment of this type is illustrated in figure 5. A dose as low as 0.1-1 μg produced almost a maximal effect in the skeletal muscles of one hind leg. A further increase in the dose of acetylcholine did not, as a rule, raise the magnitude[3] of the increase in blood flow appreciably, but merely prolonged its duration[4] somewhat. Stimuli of varying intensity produced vasodilator responses of similar appearance. The threshold value was about 1.0 volt in this case. A virtually maximal increase of flow was brought about at 3.5 volts. A further increase of the intensity to 5.0 volts produced no further rise in the blood flow.

Following atropinization, further stimulation no longer gave rise to any increase of blood flow.

Stimulation Frequency

The frequency of stimuli usually amounted to 70 per second. In some cases, the frequency was varied in order to elucidate the optimum with respect to the magnitude of the vasodilator responses. An experiment of this kind is illustrated in figure 6. With the intensity of stimuli (2.5 volts) and duration of individual impulses (2 milliseconds) used there, the lower threshold value for the frequency was about 20 per second. In other experiments, increasing the intensity was found to elicit manifest responses

[1] The type of ordinate recorder employed did not give a recording that was inversely proportional to the rate of drip. The scales in milliliters per minute, given in the figures, are empirical. On the scales have been uniformly marked the values for the velocity of flow, an exponential distribution of which has been taken: 2^{-2}, 1.5×2^{-2}, 2^{-1}, ... 1.5×2^{3}, 2^{4}. In figure 5, for example, the scale thus became 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 ml per minute.

[2] As guidance for quantitative evaluation of the circulation in the sectors of tissue studied, the following approximate weights may be mentioned (cat 3.0 kg):

Fore paw (to ankle level)	30-35 gm
Hind paw („ „ „)	40-45 gm
Skinned foreleg (from ankle to middle of upper arm)	70-80 gm
Skinned hind leg („ „ „ „ „ thigh)	110-130 gm

[3] By "magnitude of the increase in blood flow" is meant here the difference (e.g. in per cent) between the maximum recorded blood flow (during temporary vasodilatation) and the initial value.

[4] By "duration of the increase in blood flow" is meant the time elapsing between the beginning of the increase and the return to the initial level.

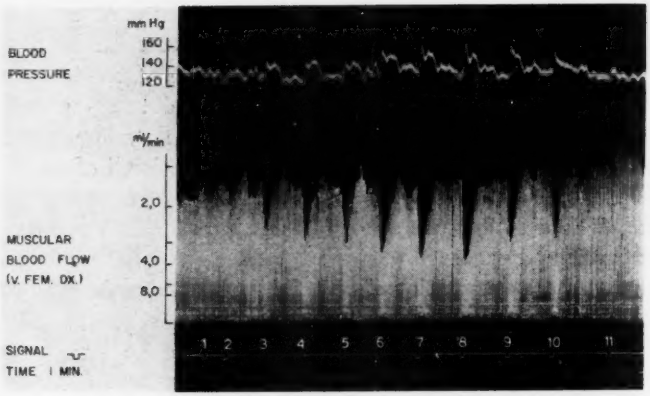


Fig. 6. Cat 2.0 kg. Dial 50 mg/kg. A. carotis commun. sin. occluded. Vasodilator responses in the muscles of the right hind leg to stimulation of varying frequency in the right part of the tectum mesencephali.

1.	Stimulation,		10/sec,	2.0	V,	10	sec.		Increase	of	flow		—
2.	„	— „	20/	„	„	„	„	„	„	„	„	<	10 %
3.	„	— „	30/	„	„	„	„	„	„	„	„		50 %
4.	„	— „	40/	„	„	„	„	„	„	„	„		70 %
5.	„	— „	50/	„	„	„	„	„	„	„	„		80 %
6.	„	— „	70/	„	„	„	„	„	„	„	„		100 %
7.	„	— „	90/	„	„	„	„	„	„	„	„		110 %
8.	„	— „	120/	„	„	„	„	„	„	„	„		130 %
9.	„	— „	180/	„	„	„	„	„	„	„	„		90 %
10.	„	— „	250/	„	„	„	„	„	„	„	„		70 %
11.	„	— „	350/	„	„	„	„	„	„	„	„	<	10 %

(Pulse duration 2 msec except in 11, where it was 1 msec.)

even at a frequency of 5-10 per second. A frequency of 50-70 per second may be regarded as the lower limit if satisfactory effects are to be obtained. The greatest effect in the above-mentioned experiment was reached with 120 per second. At frequencies exceeding about 200 per second the responses decreased.

Pulse Duration

Figure 7 shows an experiment designed to illustrate the significance of the individual impulse at a constant frequency—70 per second—and intensity of stimuli—2.5 volts. The best results, as will be seen, were reached with impulse durations of between 0.5 and 5 milliseconds.

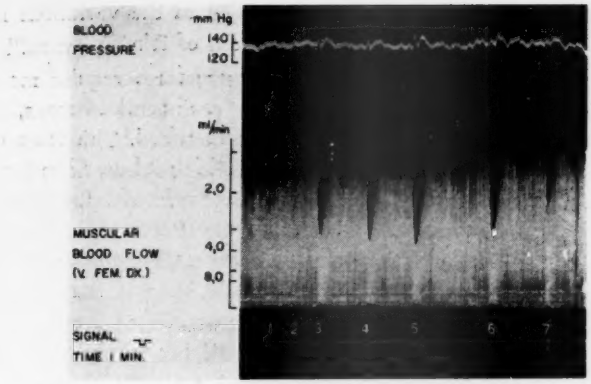


Fig. 7. Cat 2.0 kg. Dial 50 mg/kg. A. carotis commun. sin. occluded. Vasodilator responses in the muscles of the right hind leg to stimulation with impulses of varying duration in the right part of the tectum mesencephali.

1.	Stimulation,		0.1	msec.	2.5	V,	10	sec.	Increase of flow			—
2.	„	—	„	0.2	„	„	„	„	„	„	„	—
3.	„	—	„	0.5	„	„	„	„	„	„	„	90 %
4.	„	—	„	1	„	„	„	„	„	„	„	100 %
5.	„	—	„	2	„	„	„	„	„	„	„	110 %
6.	„	—	„	5	„	„	„	„	„	„	„	110 %
7.	„	—	„	10	„	„	„	„	„	„	„	50 %

(Frequency 70/sec except in 7, where it was 35/sec.)

Duration of Stimulation

The duration of stimulation was generally between 10 and 20 seconds. With durations shorter than 10 seconds only a minor increase in flow resulted. Increasing the duration above 20-30 seconds, on the other hand, did not raise either the magnitude of the responses or the duration to a corresponding degree. When the stimulation had terminated and, in the case of prolonged stimulation, during it, the blood flow returned to the initial level within the course of a minute or so.

Comment

The vasodilator responses did not diverge in appearance and character from those described in hypothalamic stimulation (Eliasson, Folkow, Lindgren and Uvnäs, 1951; Eliasson, Lind-

GREN and UVNÄS, 1952). The same applied to the variations in respect of different intensities and durations of stimuli.

It is a well-known fact that central structures require more powerful electrical stimulation than do peripheral neurons, if equivalent peripheral responses are to be obtained. This is especially true of the frequency of stimuli. These problems have been studied in detail by PITTS *et al.* (BRONK, PITTS and LARRABEE, 1939; PITTS, LARRABEE and BRONK, 1941; PITTS and BRONK, 1942). They used stimulation in the hypothalamus and recorded the impulse frequency in single preganglionic fibers of the cervical sympathetic at varying frequencies and intensities of stimulation. It rose with increased frequency of stimuli but, at a moderate intensity, did not amount to more than 6 per second when the stimuli had a frequency of 100 per second. Similarly, the peripheral impulse frequency might increase if the intensity of stimuli rose (with a constant frequency); variation of the intensity at a frequency of 100 per second gave a peripheral variation of between 1 per 2 seconds and 10 per second.

The results reported by these authors, together with the fact that increased intensity of stimulation must give a greater spread of stimuli and hence involve more neurons, should explain why, in the experiments reported here, mounting intensity was associated with a greater increase of the blood flow in the muscles.

Bearing in mind the substantial reduction of the postganglionic frequency in relation to the frequency of stimuli, the threshold value—5-20 per second—obtained for the latter at a moderate intensity also appears to be plausible. It is mentioned above (Chapter I) that the impulse frequency in sympathetic postganglionic vasoconstrictor fibers probably does not exceed 6-8 per second under physiological conditions. Similar observations have been made as regards sympathetic vasodilator fibers (FOLKOW, 1952). In view of these results and those of PITTS *et al.* it seems reasonable that the optimal frequency of mesencephalic stimulation (70-150 per second) may cause physiologically maximal firing of postganglionic vasodilator fibers.

It is not clear why the responses decreased when the frequency of stimuli rose above a certain optimum. Several explanations are

conceivable. An increase in the frequency of stimuli may result in high-frequency block at synapses. Further, the possibility must be considered that at higher frequencies polarization may occur at the electrode tip, resulting in increased electrode resistance and decreased effect of the stimulation (decrease of pulse current). In an investigation of rises in blood pressure as a result of stimulation in the hypothalamus, similar observations regarding a frequency optimum were made by HARE and GEOHEGAN (1939, 1941). (The problem of reversal effects is discussed in section 3.)

An elicited increase of blood flow, as mentioned above, could not be maintained during prolonged stimulation. A major cause might have been increasing polarization at the electrode.

3. Character and Magnitude of Other Vascular Responses

Coincidently with increases of flow in the skeletal muscles upon stimulation in tectal regions, decreases occurred in other vascular areas such as cutaneous and visceral zones. As regards the influence of stimulation frequency and duration of impulses, these vasoconstrictions showed much the same behavior as the vasodilatation. The variations of vasoconstriction in the skin at different frequencies of stimuli are shown in figure 8.

There was no major deviation, with regard to intensity of stimuli, from the data for vasodilatation in the muscles. However, at high intensities the more pronounced vasoconstriction in the above-mentioned areas was reflected in the blood pressure response, pronounced rises being observed. This means that with stimuli of high intensity the vasoconstrictor components predominated. At the same time, evaluation of the responses was made difficult in that the rises of blood pressure became important factors in the changes of blood flow.

As regards the blood pressure response, reversals were observed too, as pointed out in section 1. Those falls of blood pressure

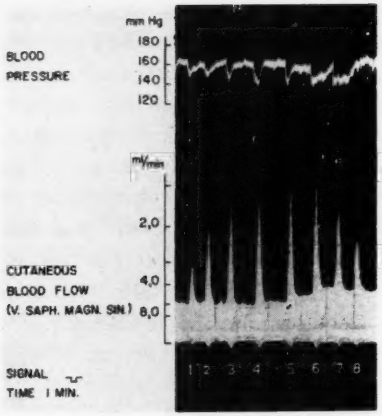


Fig. 8. Cat 4.8 kg. Dial 40 mg/kg. Aa. carotides commun. occluded. Vasoconstrictor responses in the skin of the left hind leg to stimulation of varying frequency in the right part of the tectum mesencephali.

1.	Stimulation,		20/sec,	2.5	V,	10	sec.		Decrease	of	flow	50 %
2.	„	—	„	30/	„	„	„	„	„	„	„	65 %
3.	„	—	„	50/	„	„	„	„	„	„	„	70 %
4.	„	—	„	70/	„	„	„	„	„	„	„	75 %
5.	„	—	„	90/	„	„	„	„	„	„	„	75 %
6.	„	—	„	120/	„	„	„	„	„	„	„	70 %
7.	„	—	„	200/	„	„	„	„	„	„	„	60 %
8.	„	—	„	400/	„	„	„	„	„	„	„	50 %

(Pulse duration 2 msec except in 8, where it was 1 msec.)

that sometimes attended the increase of flow in the muscles at low intensities of stimuli, almost invariably changed into rises when the voltage increased enough. The critical intensity of stimulation varied greatly from one animal to another.

Comment

In the literature there are occasional reports of reversal effects, usually in the case of hypothalamic stimulation; i.e., by varying the intensity and frequency of stimuli, a depressor effect may be converted into a pressor effect (HARE and GEOHEGAN, 1939, 1941; BRONK, PITTS and LARRABEE, 1939; PITTS, LARRABEE and BRONK, 1941; PITTS and BRONK, 1942; BERRY, MCKINLEY and

HODES, 1942; MCQUEEN, BROWNE and WALKER, 1954). As regards variation of the intensity, similar phenomena were also observed in mesencephalic stimulation in the present investigation.

Since the impulse frequency in the peripheral neurons is correlated to both the intensity and frequency of the central stimulation, intensity reversal and frequency reversal are closely linked to each other. One of the theories propounded to explain the frequency reversal is the following: Artificial central stimulation, regardless of frequency, completely suppresses the spontaneous activity in peripheral sympathetic (vasoconstrictor) fibers. If as a result—depending on parameters of stimulation—the peripheral impulse frequency is lower than the spontaneous, the consequence will be lower vascular tone and a fall of blood pressure. If the peripheral impulse frequency is higher, the blood pressure will rise. It follows that the critical reversal frequency will vary from one case to another and will be dependent on the spontaneous vasoconstrictor tone of the animal. These problems were discussed more extensively by STRÖM (1950 a, b). Since even a variation of the stimulation intensity at a constant frequency may produce major variations of the peripheral impulse frequency, the above theory may well explain the intensity reversal too.

However, since both vasoconstrictor and vasodilator neurons are now known to exist in the brain stem, it is also conceivable that such changes in the blood pressure response could be due to interaction between vasoconstrictor and vasodilator activity. The present investigation affords no evidence that this interaction may consist in activation of the different neurons at different parameters of stimulation. On the other hand, the blood pressure reversal attending increased intensity of stimulation could be explained by postulating a greater spatial extension of vasoconstrictor neurons than of vasodilator neurons. In this case it is conceivable that with increasing intensity of stimulation, and hence spread of stimuli, the number of activated vasoconstrictor neurons continues to rise after all vasodilator neurons have come within the field of stimulation, so that the relative numbers of activated neurons of the two types will change.

4. Peripheral Distribution of the Vascular Responses

Skeletal Muscles

There is much to indicate, as discussed below (sections 5 and 7), that the increases of blood flow elicited by electrical stimulation in tectal regions are due to activation of sympathetic cholinergic vasodilator nerves. That the latter may be activated by central stimulation was shown by ELIASSON, FOLKOW, LINDGREN and UVNÄS (1951), whose findings were verified in several later investigations (ELIASSON, LINDGREN and UVNÄS, 1952; LINDGREN and UVNÄS, 1953 a, b; and others). In these investigations it was chiefly cortical, hypothalamic and medullary regions that were stimulated. It seems likely, therefore, that in the present experiments the vasodilatations resulted from stimulation of the mesencephalic portion of the intracerebral sympathetic vasodilator pathway. Stimulation in the anterior hypothalamus of the cat elicits, as shown by ELIASSON, FOLKOW, LINDGREN and UVNÄS (1951), general vasodilatation in all skeletal muscles, or at all events in all four extremities. On the other hand, activation of sympathetic vasodilator neurons in the medulla oblongata elicits only unilateral responses (LINDGREN and UVNÄS, 1953 b). In view of these findings, great interest attaches to the peripheral extension of vasodilator responses to mesencephalic stimulation.

Numerous experiments in the present investigation showed that the increases of blood flow occurring in the skeletal muscles on stimulation in the tectum opticum were virtually always bilateral. They were usually of the same order of magnitude, though occasionally a quantitative difference could be observed, the responses being somewhat greater in the ipsilateral than in the contralateral limbs. A typical experiment is illustrated in figure 9. Here the blood flow was recorded concurrently in the two skinned hind legs. Stimulation of a point in the right side of the tectum mesencephali with 2.5 and 3.0 volts respectively produced marked increases of blood flow in both extremities. Of further interest is the blood pressure curve. The stimulations (1 and 2 in figure 9) were attended by slight rises of blood pressure; otherwise the curve is quite regular. After 0.2 mg atropine per kg, which almost

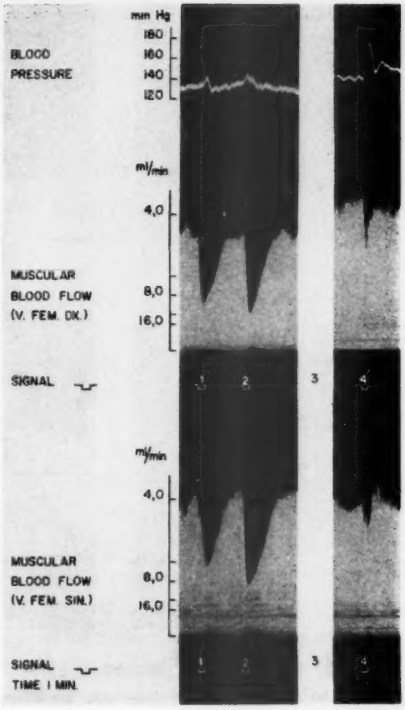


Fig. 9. Cat 3.4 kg. Dial 50 mg/kg. A. carotis commun. sin. occluded. Vasodilator responses in the muscles of both hind legs to stimulation in the right part of the tectum mesencephali.

1. Stimulation, 2.5 V, 15 sec.
2. „ — „ 3.0 „ „ „
3. Atropine 0.2 mg/kg I.V.
4. Stimulation, 3.0 V, 15 sec.

completely blocked the vasodilator effect of stimulation, the blood pressure response changed. A quite distinct rise of blood pressure occurred. The relevant experiment provides no explanation of this, but it seems plausible to assume that vasoconstrictor neurons to other parts of the organism were activated coincidently with the vasodilator nerves to the skeletal muscles. After blocking of the vasodilator responses with atropine, the vasoconstriction was able to manifest itself and affect the blood pressure.

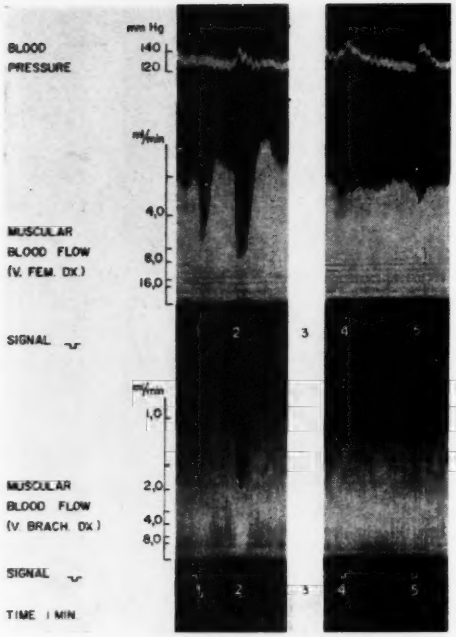


Fig. 10. Cat 2.6 kg. Dial 50 mg/kg.
A. carotis commun. sin. occluded. Nn. vagi cut. Artificial respiration. Vasodilator responses in the muscles of the right hind leg and the right foreleg to stimulation in the right part of the tectum mesencephali.

1. Stimulation, 2.0 V, 10 sec.
2. „ — „ 3.0 „ „ „
3. Atropine 0.2 mg/kg I.V.
4. Stimulation, 2.0 V, 10 sec.
5. „ — „ 3.0 „ „ „

The result of a similar experiment is shown in figure 10, the difference being that in this case the blood flow was studied in the muscles of one hind leg and the corresponding foreleg. The results show that the increases of flow produced in the skeletal muscles by mesencephalic stimulation were not local but appeared to be generalized; at all events they occurred coincidently in the extremity muscles. Other skeletal muscle regions are more difficult to isolate for blood flow determination by the method employed here, and no such experiments were attempted.

In some experiments in which deeper structures in the pons were stimulated, characteristic vasodilatation was sometimes elicited from there. A noteworthy finding was, however, that such effects generally had only an ipsilateral distribution.

Other Vascular Areas

The vasodilator responses were often attended by minor pressor effects that became more pronounced when the former had been blocked with atropine. Sometimes, moreover, an earlier fall of blood pressure after atropine was converted into a rise. With a view to studying the cause of the pressor effects the blood flow in another vascular area was recorded, in several experiments, concurrently with the blood flow in the muscles of a leg. Figure 11 shows the responses in the muscles of the right hind leg and in the skin of the left hind paw. The differences in reactions are striking. Coincidently with the vasodilatation in the muscles there was pronounced constriction of cutaneous vessels. The decrease of flow in the skin must obviously have been due to real vasoconstriction; for it was unchanged after blocking of the muscle vasodilatation with atropine, and could not, therefore, have been of compensatory nature. In this case the stimulated point in the tectum opticum was 3 mm to the right of the midline, and the cutaneous blood flow was recorded in the left hind leg. The result may suggest that the vasoconstrictor effects in the skin have a bilateral distribution, like the vasodilator effects in the muscles. The correctness of this assumption is evident from figure 12, where the blood flow was recorded in both hind paws.

Another major vascular area where a decrease of blood flow occurred parallel with the increased flow in the skeletal muscles was the intestinal region. Observations of intestinal blood flow showed that vasoconstriction in this region was at least as great as that in the skin (figure 13).

It seems evident that the vasoconstriction occurring in the skin and intestines had an important bearing on the blood pressure response; for the skeletal muscles constitute a substantial part of the total vascular area, and hence it seems reasonable to assume that pronounced vasodilatation there would be manifested in a

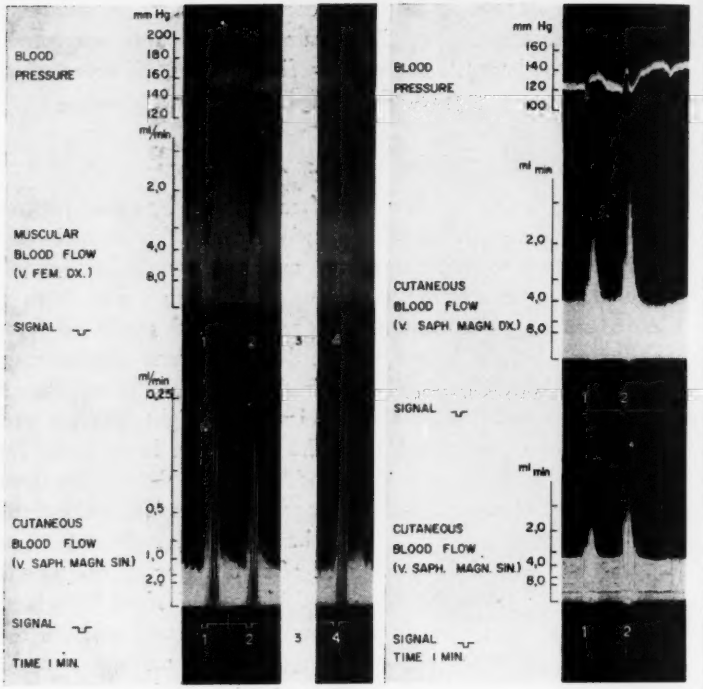


Fig. 11. Cat 2.5 kg. Dial 50 mg/kg.

Adrenals removed. Aa. carotides commun. occluded. Artificial respiration. Vasodilator responses in the muscles of the right hind leg and vasoconstrictor responses in the skin of the left hind leg to stimulation in the right part of the tectum mesencephali.

1. Stimulation, 3.5 V, 15 sec.
2. „ — „ „ „ „ „
3. Atropine 0.2 mg/kg I.V.
4. Stimulation, 3.5 V, 15 sec.
5. „ — „ „ „ „ „

Note the persisting vasoconstrictor response after atropinization.

Fig. 12. Cat 3.4 kg. Dial 55 mg/kg.

Vasoconstrictor responses in the skin of both hind legs to stimulation in the right part of the tectum mesencephali.

1. Stimulation, 2.0 V, 10 sec.
2. „ — „ 2.5 „ 15 „

Note the reversal of the blood pressure response with increasing voltage and duration.

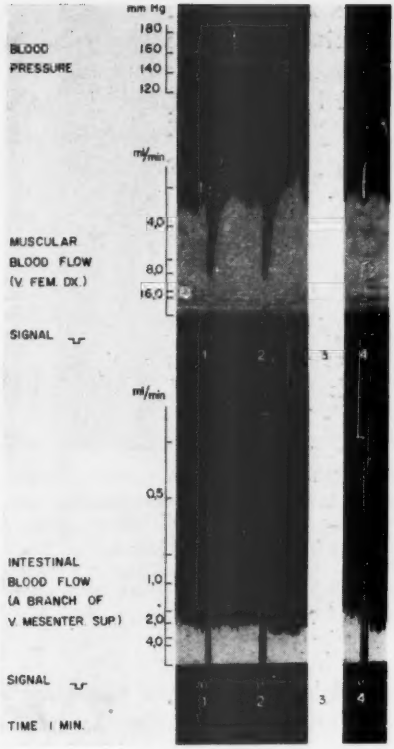


Fig. 13. Cat 2.5 kg. Dial 40 mg/kg.
Aa. carotides commun. occluded. Nn. vagi cut.
Vasodilator responses in the muscles of the right hind leg and vasoconstrictor responses in the intestine to stimulation in the right part of the tectum mesencephali.

1. Stimulation, 3.0 V, 10 sec.
2. „ — „ „ „ „ „
3. Atropine 0.2 mg/kg. I.V.
4. Stimulation, 3.0 V, 10 sec.

Note the persisting vasoconstrictor response after atropinization.

distinct fall of blood pressure. With the aim of investigating the role of vasoconstriction in the total response, an experiment of the following type was conducted (figure 14). After vasodilatation had been produced in the hind-leg muscles by mesencephalic stimulation, influence from the vascular bed in the intestines was eliminated. This was done by functional evisceration consisting

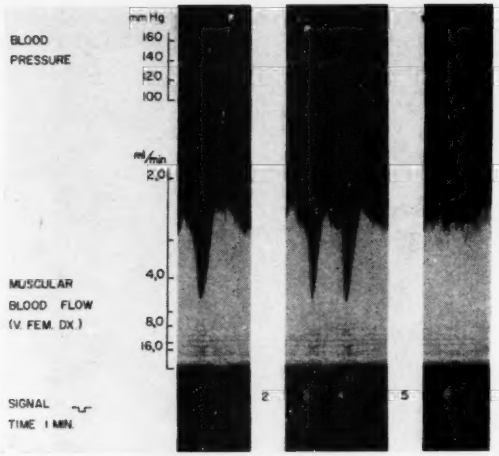


Fig. 14. Cat 2.9 kg. Dial 55 mg/kg. A. carotis commun. sin. occluded. Vasodilator responses in the muscles of the right hind leg to stimulation in the right part of the tectum mesencephali before and after evisceration.

1. Stimulation, 2.5 V, 10 sec.
2. Evisceration.
3. Stimulation, 2.5 V, 10 sec.
4. Stimulation, 2.5 V, 10 sec.
5. Atropine 0.3 mg/kg I.V.
6. Stimulation 2.5 V, 10 sec.

Note the fall of blood pressure on stimulation after evisceration.

in clamping off the large arteries and veins (superior and inferior mesenteric) with forceps, and likewise the duodenum below the pylorus and the rectum a few centimeters above the anus. At the start of the experiment the four paws had already been deprived of their circulation by tight ligatures above the ankles, in order to reduce the cutaneous area. The increase of blood flow in the hind-leg muscles was practically unchanged after evisceration. However, marked falls of blood pressure now occurred. With the elimination of large vascular areas where vasoconstriction might occur, the vasodilatation component now predominated.

Comment

It is interesting that the apparently general vasodilatation in the skeletal muscles was often associated with an equally general vasoconstriction in skin and intestines. This implies that the

responsive structures in the mesencephalon consisted of both vasoconstrictor and vasodilator neurons. It does not necessarily follow, however, that with an improved stimulation technique the vasodilator neurons would not be stimulated selectively. In point of fact it has been reported that vasodilator neurons in the canine hypothalamus can be stimulated selectively with the technique used here, without coincident vasoconstrictor effects (ELIASSON, LINDGREN and UVNÄS, 1952). In cats, on the other hand, hypothalamic stimulation usually brought about a response pattern of vasodilatation in skeletal muscles and vasoconstriction in skin and gut (ELIASSON, FOLKOW, LINDGREN and UVNÄS, 1951), resembling that described here in respect of mesencephalic stimulation.

No vasodilatation whatsoever was observed in cutaneous and splanchnic areas. The vasodilatation in the skeletal muscles, as shown in section 5, was effected by sympathetic vasodilator nerves. The results constitute further evidence that such nerves are distributed only to that tissue. They confirm, moreover, a similar view that FOLKOW and UVNÄS (1948 b) propounded on the basis of the results of peripheral stimulation of sympathetic neurons.

5. Mechanism of the Vasodilator Responses and Efferent Pathways of the Vasodilator Impulses

Having regard to the discussion, which is still going on, as to nervous and humoral vasodilatation, the reported vasodilator effects in the skeletal muscles require further experimental analysis.

Muscle Activity—Mechanical and Metabolic Factors

In the present investigation, muscle activity sometimes attended stimulation in the tectum opticum. Slight and irregular activity of this kind could occur in the extremities, notably when more ventral structures were stimulated. It is naturally

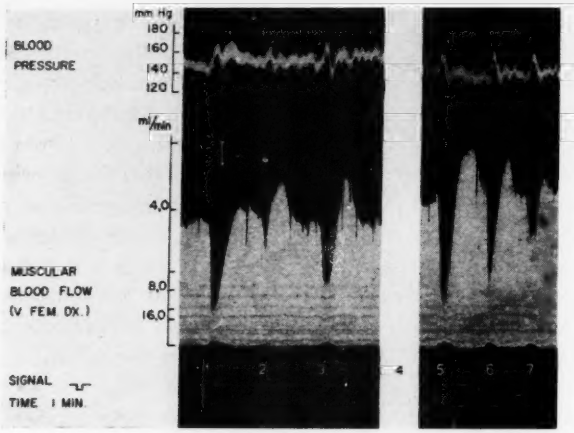


Fig. 15. Cat 2.8 kg. Dial 40 mg/kg. A. carotis commun. sin. occluded. Vasodilator responses in the muscles of the right hind leg to stimulation in the right part of the tectum mesencephali before and after ligation of the spinal medulla.

1. Stimulation, 3.0 V, 15 sec.
2. „ — „ 1.0 „ „ „
3. „ — „ 2.0 „ „ „
4. Lig. of the spinal medulla at L_5.
5. Stimulation, 3.0 V, 15 sec.
6. „ — „ 2.0 „ „ „
7. „ — „ 1.0 „ „ „

Note that the vasodilator responses are unchanged after ligation of the spinal medulla.

conceivable that in such cases the muscle contractions contributed to the increase of blood flow. For the purpose, among other things, of excluding this possibility, experiments were conducted on animals whose spinal medulla had been ligated at the level of L_5. Both hind legs had thus been decentralized in the somatomotor sense, but had an intact sympathetic innervation. The increases of blood flow elicited were unchanged after this operation (see figure 15).

Adrenaline

It is known that stimulation of some parts of the brain stem, e.g. the hypothalamus, may cause activation of the splanchnic nerves, followed by secretion of catechols from the adrenals (e.g.,

FOLKOW and EULER, 1954). Since adrenaline in low concentrations has a dilator effect on muscle vessels but a constrictor effect on cutaneous and intestinal vessels (FOLKOW, FROST and UVNÄS, 1948), it is conceivable that a secretion of adrenaline could give rise to, or at all events contribute to, the observed increases of blood flow in skeletal muscles. That this mechanism alone lay behind the responses is impossible, however, since numerous experiments were conducted upon animals in which the adrenals had either been removed or denervated (see e.g. figure 16). Nevertheless, an increase of the secretion of adrenaline might be a contributory factor, albeit a minor one. Figure 17 shows another experiment in which one adrenal was eliminated during the course of the experiment (the other had been removed at the outset). The vasodilator responses in the muscles were, as will be seen, fairly unaffected by this measure. (The problem of coincident adrenal activation is studied further in section 9.)

Antidromic Vasodilator Impulses in the Dorsal Roots

In recent years a number of observations have been made which show unequivocally that antidromic vasodilator impulses play no part whatsoever in central vasomotor control (FOLKOW, STRÖM and UVNÄS, 1950; LINDGREN and UVNÄS, 1954 a). The results of the reported experiment (figure 15) in which the spinal medulla was ligated at L_5 exclude the antidromic vasodilator impulses, too, from the discussion.

Inhibition of the Tone of Sympathetic Vasoconstrictor Nerves

This problem has a close bearing upon the significance of the baroceptor mechanisms in the responses described. It has been mentioned in the foregoing (see e.g. section 1) that the blood pressure response to stimulation which increased the blood flow in the muscles, often consisted in a rise due to predominance of the coincident vasoconstrictions in the cutaneous and splanchnic areas. In these cases the muscle vasodilatation might, therefore, have resulted partly from activation of the baroceptor mechanisms. However, several of the reported experiments show that

similar dilatation of muscle vessels could even be produced after baroceptors have been functionally eliminated (bilateral vagotomy and bilateral denervation of the carotid sinus or occlusion of both carotid arteries) (see e.g. figure 13). In point of fact, the recorded increases of blood flow in such cases were often greater, since vasoconstrictor tone rose and the blood pressure adjusted itself at a higher level. The baroceptor mechanisms accordingly seem to have had no qualitative influence on the observed vasodilatations. The role of these mechanisms will be discussed, however, in greater detail later on (Chapter V: 2).

The blocking effect of atropine, as mentioned in the foregoing, was taken as a criterion that the increases of blood flow elicited in the skeletal muscles by mesencephalic stimulation were of uniform type. Such an effect of atropine may be seen in a number of the experiments illustrated. In the doses employed—0.1-0.3 mg per kg—atropine has only peripheral effects and, according to earlier investigations, no influence on known types of vasoconstrictor inhibition, such as depressor reflexes caused by sinus or vagus nerve activation (LINDGREN and UVNÄS, 1955), or depressor responses following direct electrical stimulation of inhibitory structures in the medulla oblongata (LINDGREN and UVNÄS 1954 a).

Vasodilatation resulting from inhibition of constrictor tone was blocked by sympatholytic substances—for instance, in reflex vasodilatation at baroceptor activation (FOLKOW and UVNÄS, 1948 b; CELANDER and FOLKOW, 1951). The vasodilatation elicited in skeletal muscles by mesencephalic stimulation was not, as shown in figure 24, influenced by Dihydroergotamine.

Hence there is no plausible reason to assume that the vasodilator responses in question here resulted from inhibition of the activity in vasoconstrictor nerves.

Sympathetic Vasodilator Nerves

In the aforementioned experiment (figure 15) in which the spinal medulla was ligated at the level of L_3, the sympathetic chain was the only nervous communication between the central

nervous system and those peripheral organs in which the increase of blood flow occurred—the skeletal muscles of the hind legs. The sympathetic chain, therefore, probably contains fibers that mediate the impulses from the mesencephalon to the periphery. If such be the case, an experiment of the opposite type might be conducted in order to investigate this question further. If the experimental animal retains the somatic innervation to the hind legs intact, but is deprived of the autonomic, i.e. sympathetic innervation to one hind leg, then, if this hypothesis is correct, no vasodilatation will occur in the sympathectomized limb. It would be difficult, however, to draw any definite conclusions from studies of the circulation in an acutely sympathectomized organ; for when the blood vessels are deprived of their tonic vasoconstrictor innervation the result will be a substantially increased blood flow. This is bound to impair greatly the ability of the blood vessels to respond to any vasodilator impulses. The vessels, it is true, will regain a part of their original tone fairly soon, but the time required for this may vary greatly from one animal to another. For such experiments, chronically sympathectomized animals were used instead, the operation usually being done 10-14 days before the acute experiment; for in this case the vessels have regained their normal tone and the blood flow has returned to its original level.

One of these experiments is illustrated in figure 16. The left hind leg had been sympathectomized 13 days previously by removal of the ipsilateral sympathetic chain in the abdomen. As in several other experiments, bilateral adrenalectomy was done at the outset. The venous blood flow was recorded in the usual way in each of the skinned hind legs. The initial blood-flow levels, as will be seen, were approximately the same in both legs. Stimulation in the tectum opticum on the right side, 3 mm from the middle line, elicited a pronounced increase of flow in the muscles of the right leg; but in the left leg there was a minor decrease. This finding can probably be attributed to purely mechanical causes. Although the blood pressure recorded in the carotid artery was fairly constant—at all events no fall was observed parallel with the stimulation—the blood pressure in the

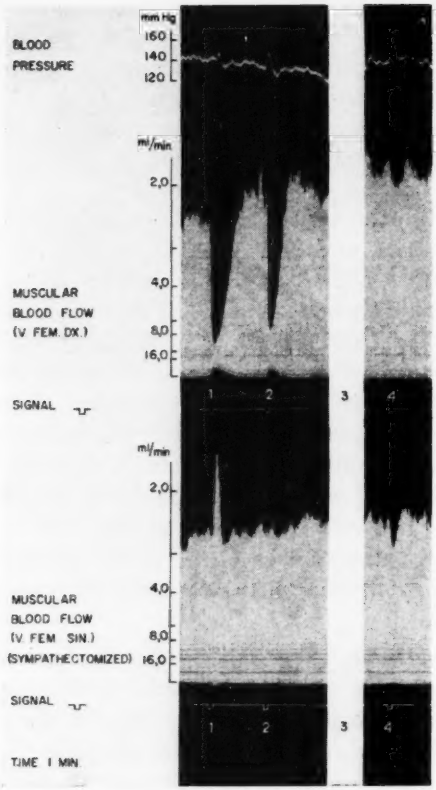


Fig. 16. Cat 3.3 kg. Dial 50 mg/kg.

Left hind leg sympathectomized 13 days before the experiment.

Adrenals denervated. A. carotis commun. sin. occluded.

Vasodilator responses in the muscles of the right hind leg to stimulation in the right part of the tectum mesencephali.

1. Stimulation, 3.0 V, 10 sec.
2. „ — „ 2.0 „ „ „
3. Atropine 2.0 mg/kg. I.V.
4. Stimulation, 2.0 V, 10 sec.

Note that no vasodilatation occurred in the sympathectomized left leg.

distal part of the aorta had probably fallen on account of the pronounced muscle vasodilatation. Since the blood flow in the (vasomotor) denervated leg passively coincided, to a large extent, with the arterial pressure, it seems plausible to regard the transient diminution of flow as a temporary blood pressure fall in the left femoral artery. When the stimulation was repeated with somewhat lesser intensity, so that the muscle vasodilatation was not so extensive, no decrease of flow occurred in the sympathectomized leg. The slight increase of flow in that leg upon stimulation after atropinization may have been passive to the rise of blood pressure.

It would thus be justified to claim that the reported increases of blood flow in the skeletal muscles were the results of nervous activity involving the sympathetic nervous system, and that they were produced by activity in sympathetic vasodilator nerves.

Comment

On the one hand, it is not surprising that the observed increases of blood flow in the skeletal muscles, as shown by the foregoing investigation, cannot be explained other than by activity in sympathetic vasodilator nerves. For the same conclusion was reached by EIASSON, FOLKOW, LINDGREN and UVNÄS (1951) and EIASSON, LINDGREN and UVNÄS (1952) with regard to similar responses to stimulation in the anterior hypothalamus, from which the efferent pathways must obviously pass the mesencephalon.

On the other hand, this special vasodilator system to skeletal muscle means that vasodilatation in that tissue can be elicited, from central structures, in two ways—a circumstance that may seem somewhat bewildering. In the first place, vasodilator nerves may be activated, and secondly vasoconstrictor tone may be inhibited, as LINDGREN and UVNÄS (1955) have also pointed out. The significance of this was discussed by those authors, and the functional implications of the two mechanisms will also be discussed further in Chapters V and VI.

6. Mechanism of the Vasoconstrictor Responses and Efferent Pathways of the Vasoconstrictor Impulses

The only generally recognized vasoconstrictor nerves are those referable to the sympathetic outflow. According to the findings reported above, the decreases of blood flow in skin and intestines following mesencephalic stimulation were caused by active vasoconstriction. In view of the uniformity of the vasoconstrictor system, the question of how this vasoconstriction was effected can be answered only in two ways: An increase of tone in vasoconstrictor nerves, or secretion of catechols from the adrenals. The possibility that the last-named factor may play a major part in the observed changes of blood flow has already been ruled out insofar as the vasodilator responses in the muscles are concerned. The same is probably true of the vasoconstrictions in other vascular areas. Usually elimination of the adrenals, as will be seen from figure 17, did not appreciably affect the decrease of blood flow in the skin. This decrease must therefore be attributed chiefly to impulses in the sympathetic vasoconstrictor nerves. In other experiments there was a slight reduction of the vasoconstrictor responses after elimination of the adrenals (figure 28).

Comment

In section 4, attention was drawn to various reasons why the observed vasoconstrictor responses were genuine effects of stimulation—i.e., activation of mesencephalic vasoconstrictor neurons—and not of secondary compensatory nature via the baroceptor mechanisms. It is important to be able to exclude these latter mechanisms, for ELIASSON, LINDGREN and UVNÄS (1952) reported that such effects often attended selective vasodilator activation by stimulation in the hypothalamus. Their experiments were performed on dogs, and the vasodilator responses were frequently accompanied by substantial falls of blood pressure. In cats, on the other hand, falls of blood pressure are less common in central activation of sympathetic vasodilator fibers, both in hypothalamic stimulation (ELIASSON, FOLKOW, LINDGREN and UVNÄS, 1951;

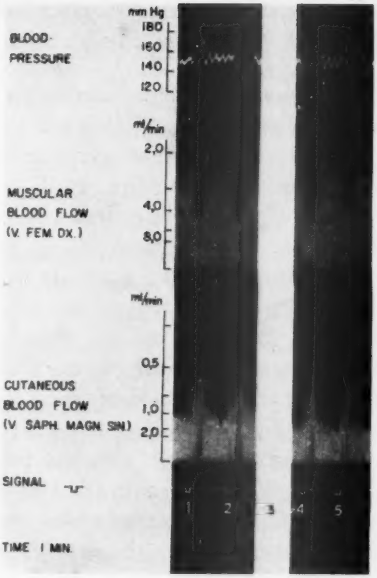


Fig. 17. Cat 2.5 kg. Dial 50 mg/kg.
Left adrenal removed. Aa. carotides commun. occluded.
Vasodilator responses in the muscles of the right hind leg and vasoconstrictor responses in the left hind leg before and after removal of the right adrenal.
1. Stimulation, 3.0 V, 10 sec. 4. Stimulation, 3.0 V, 10 sec.
2. „ — „ „ „ „ „ 5. „ — „ „ „ „ „
3. Right adrenal removed.
Note that the vasomotor responses are practically unchanged after removal of the right adrenal.

Folkow and Gernandt, 1952) and in mesencephalic stimulation —a finding that points to coincident vasoconstrictor activation. (The role of the baroceptor mechanisms will be discussed further in Chapter V: 2.)

It has emerged, too, that the adrenals play only an inconsiderable role in the vasoconstrictor responses. (In section 9, further light is thrown on the problem of adrenal activation in mesencephalic stimulation.)

7. Peripheral Transmission of the Vasodilator Impulses

The designations "adrenergic" and "cholinergic" for sympathetic fibers were introduced by DALE (1934). With respect to the transmission at sympathetic vasodilator nerve endings, a spirited discussion has since been going on. The distribution of the two types has been considered to vary in different species of animals. The cat has been regarded as having both adrenergic and cholinergic vasodilator fibers (BÜLBRING and BURN, 1935; ROSENBLUETH and CANNON, 1935). The entire problem complex of adrenergic vasodilator nerves has been the subject of further extensive investigations in recent years and many authors, as mentioned in Chapter I, now doubt the existence of them (for references, *vide* FOLKOW and UVNÄS, 1950).

Of particular interest are some observations by FOLKOW, HAEGER and UVNÄS (1948) and FOLKOW and UVNÄS (1950). They found that stimulation of the sympathetic chain in the abdomen elicited an increase of blood flow in the muscles of the hind legs of ergotaminized cats. Eserine potentiated and atropine blocked the effects. A substance with acetylcholine-like properties was demonstrable in perfusate. On the other hand the same authors absolutely disputed the existence of adrenergic vasodilator fibers.

No evidence of central representation of sympathetic adrenergic vasodilator nerves seems to have been presented. But it has been shown, as mentioned above, that electrical stimulation in the hypothalamus and medulla oblongata may activate sympathetic dilator nerves, probably of cholinergic type, to the muscles in the cat (ELIASSON, FOLKOW, LINDGREN and UVNÄS, 1951; LINDGREN and UVNÄS, 1953 b). These authors adduced, as evidence of the cholinergic transmission, the effect of atropine, whose blocking action on responses due to activity in cholinergic vasodilator nerves was well-known from experiments with peripheral stimulation.

Effect of Atropine

In the present investigation, too, the blocking effect of atropine was taken as a characteristic of the vasodilator effects. In order

to throw further light on the antagonistic influence of atropine, it was investigated, even quantitatively, in a series of experiments. The result of one such experiment is shown in figure 18. Repeated stimulation in the mesencephalon produced, with mounting degrees of atropinization, decreasingly small increases of the flow from the muscles of the right hind leg. Even a comparatively small dose—0.01 mg atropine per kg—had a significant effect, reducing the increase of flow from 250 to 100 per cent. After 0.03 mg per kg the same stimulation produced an increase of flow amounting to 50 per cent. After further atropinization with a total of 0.18 mg per kg, renewed stimulation evoked only a minimal increase of flow, which probably was not due to active vasodilatation but was passive to the slight rise in blood pressure. Other experiments of similar type showed that the lower limit for a demonstrable effect of atropine on increases of blood flow under stimulation of medium intensity, was 0.005-0.01 mg per kg. Almost complete blocking was reached in most cases with 0.1-0.3 mg per kg, even when stimuli of high intensity were used. (It should be mentioned that in these experiments adrenalectomy had been done in order to preclude any possibility of effects from secreted adrenaline and noradrenaline.)

If increases of blood flow are suspected to have been caused by activity in cholinergic nerves, then it will be of interest to compare them with increases produced by intra-arterial injection of acetylcholine (see figure 5). It emerged that almost a maximal effect in one hind leg could be attained by intra-arterial injection of 0.1-1 μg acetylcholine. An increase of flow in the muscles, produced in this way, can be reduced or blocked by such doses of atropine that, similarly, influence an increase of flow resulting from mesencephalic stimulation. Figure 19 shows how the effect of 0.25 μg acetylcholine, injected into the femoral artery, was reduced by mounting doses of atropine. After 0.18 mg atropine per kg, 0.25 μg acetylcholine, which in an intact animal increased the blood flow by 180 per cent, no longer had any effect. If, on the other hand, the amount of acetylcholine injected was raised, substantially larger doses of atropine were required for complete block. To produce total inhibition of the increase of blood flow after e.g. 10 μg acetylcholine, 2-4 mg atropine per kg was required, i.e., a very large dose.

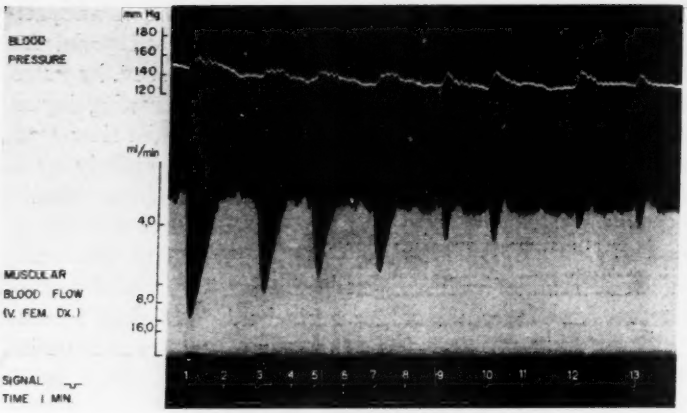


Fig. 18. Cat 3.4 kg. Dial 45 mg/kg.

Adrenals removed. A. carotis commun. sin. occluded. Nn. vagi cut.

Vasodilator responses in the muscles of the right hind leg to stimulation in the right part of the tectum mesencephali. Effect of increasing doses of atropine.

1. Stimulation, 2.5 V, 10 sec.	Increase of flow	250 %
2. Atropine 0.01 mg/kg I.V.		
3. Stimulation, 2.5 V, 10 sec.	„ „ „	100 %
4. Atropine 0.01 mg/kg I.V.		
5. Stimulation, 2.5 V, 10 sec.	„ „ „	60 %
6. Atropine 0.01 mg/kg I.V.		
7. Stimulation, 2.5 V, 10 sec.	„ „ „	50 %
8. Atropine 0.05 mg/kg I.V.		
9. Stimulation, 2.5 V, 10 sec.	„ „ „	< 20 %
10. „ — „ „ „ „ „	„ „ „	< 20 %
11. Atropine 0.10 mg/kg I.V.		
12. Stimulation, 2.5 V, 10 sec.	„ „ „	< 10 %
13. „ — „ „ „ „ „	„ „ „	< 10 %

To the assumption that atropine blocks the effect on the muscle blood flow in mesensephalic stimulation because of a peripheral cholinergic transmission mechanism, the objection may naturally be raised that the action of atropine could be central. However, the doses employed here were so small that such an explanation is most unlikely. In order to rule out this possibility that part of the atropine effect might be central, two cross-circulation experiments were conducted. Here an isolated hind leg was perfused with blood from another animal; only the nervous pathway, the ischiatic nerve, was intact. In these experiments vasodilatation

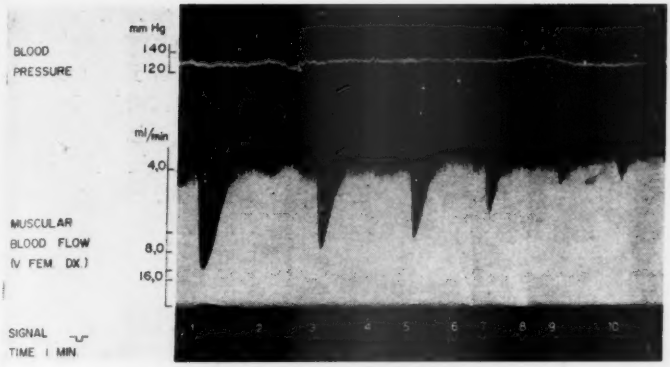


Fig. 19. Cat 3.0 kg. Dial 40 mg/kg.

Vasodilator responses in the muscles of the right hind leg to intra-arterial (a.fem.dx.) injections of acetylcholine. Effect of increasing doses of atropine.

1. Acetylcholine 0.25 μg, 0.05 ml, I.A.	Increase of flow			180 %
2. Atropine 0.01 mg/kg I.V.				
3. Acetylcholine 0.25 μg, 0.05 ml, I.A.	„	„	„	90 %
4. Atropine 0.02 mg/kg I.V.				
5. Acetylcholine 0.25 μg, 0.05 ml, I.A.	„	„	„	60 %
6. Atropine 0.05 mg/kg I.V.				
7. Acetylcholine 0.25 μg, 0.05 ml, I.A.	„	„	„	30 %
8. Atropine 0.10 mg/kg I.V.				
9. Acetylcholine 0.25 μg, 0.05 ml, I.A.	„	„	„	< 10 %
10. Saline 0.05 ml I.A.	„	„	„	< 10 %

was elicited in the muscles by the usual mesencephalic stimulation. The blood flow in the two hind legs was recorded separately, the left leg being intact and the right one isolated and perfused from the donor cat (figure 20). Atropine in a dose of 0.2 mg per kg in the donor animal totally abolished the vasodilatation in the right leg but the responses in the left one remained unchanged.

In order to find out whether the atropine effect was dependent on the anesthesia, acutely decerebrated animals were also subjected to stimulation experiments. Decerebration was done under ether anesthesia. Blood pressure, vascular tone and blood flow were found to be of approximately the same type as in anesthetized animals. Similarly, the increases of blood flow on mesencephalic or bulbar stimulation (in these animals it was simplest, for technical reasons, to apply the stimuli caudal to the mesencephalon) had the same character, and the

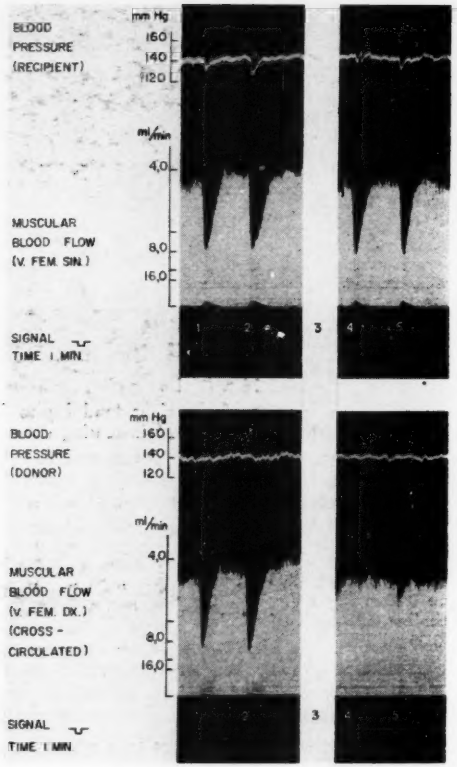


Fig. 20. Cross-circulation.
Recipient cat 3.3 kg. Dial 45 mg/kg.
Donor cat 2.6 kg. Dial 45 mg/kg. Aa. carotides commun. occluded.
Vasodilator responses in the muscles of the left (not cross-circulated) and right (cross-circulated) hind legs to stimulation in the right part of the tectum mesencephali.

1. Stimulation, 2.0 V, 10 sec.
2. „ — „ 2.5 „ „ „
3. Atropine 0.1 mg/kg I.V. to the donor.
4. Stimulation, 2.0 V, 10 sec.
5. „ — „ 2.5 „ „ „

Note the disappearance of the vasodilator responses in the cross-circulated leg after atropine.

effect of atropine was unchanged. Figure 21 shows an experiment of this kind in which stimulation was given in the pons—which explains why the responses were unilateral.

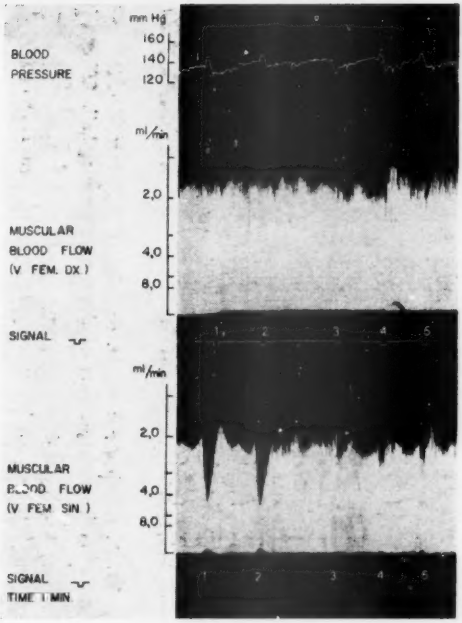


Fig. 21. Cat 2.6 kg. Decerebration 2 hours before the experiment.
A. carotis commun. sin. occluded.
Vasodilator responses in the muscles of the left hind leg to stimulation in the left part of the medulla oblongata.

1. Stimulation, 2.0 V, 15 sec.
2. „ — „ „ „ „ „
3. Atropine 0.1 mg/kg I.V.
4. Stimulation, 2.0 V, 15 sec.
5. „ — „ „ „ „ „

Note that the vasodilator responses and the effect of atropine in an unanesthetized decerebrate cat are similar to the effects in cats under anesthesia.

Effect of Eserine

Cholinesterase-inhibiting substances have also been used earlier for investigation of the chemical nature of a transmission mechanism. These substances potentiate responses via sympathetic vasodilator nerves activated by stimulation of the sympathetic chain (ROSENBLUETH and CANNON, 1935; FOLKOW, HAEGER and UVNÄS, 1948). It seemed plausible, therefore, to study the effect of such substances on the vasodilatations observed in this investigation. A reversible cholinesterase inhibitor—eserine—was chosen,

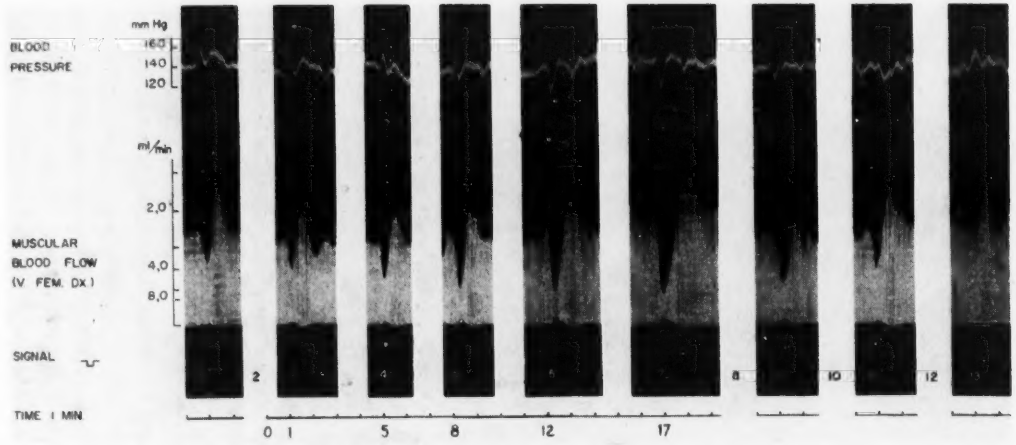


Fig. 22. Cat 3.0 kg. Dial 45 mg/kg. A. carotis commun. sin. occluded.
Vasodilator responses in the muscles of the hind leg to stimulation in the right part of the tectum mesencephali. Effect of eserine.

1. Stim., 1.25 V, 10 sec. Increase of flow 50 %
2. Eserine 0.1 mg/kg I.V.
3. Stim., 1.25 V, 10 sec. „ „ „ 50 %
4. „ „ „ „ „ „ „ „ 70 %
5. „ „ „ „ „ „ „ „ 130 %
6. „ „ „ „ „ „ „ „ 170 %
7. „ „ „ „ „ „ „ „ 260 %
8. Atropine 0.2 mg/kg I.V.
9. Stim., 1.25 V, 10 sec. Increase of flow 110 %
10. Atropine 0.3 mg/kg I.V.
11. Stim., 1.25 V, 10 sec. „ „ „ 70 %
12. Atropine 0.5 mg/kg I.V.
13. Stim., 1.25 V, 10 sec. „ „ „ 20 %

Note the potentiating effect of eserine and the large doses of atropine necessary for abolishing the vasodilator responses.

partly because it had been used by earlier workers in studies of the transmission mechanism of sympathetic vasodilator nerves. However, these attempts to demonstrate the effect of eserine encountered several difficulties. One of them was that of so adjusting the intensity of stimuli that distinct and duplicable vasodilatation would be obtained, yet would still be of as small an extent as possible; for with the intensities usually employed, the increases of blood flow were so great that no demonstrable rise in them could be expected. Figure 22 shows the effect of eserine, 0.1 mg per kg, on vasodilatation resulting from mesencephalic stimulation. The stimulation intensity of 1.25 volts was close to the threshold value. The increase of flow before administration of eserine amounted to about 50 per cent. After eserine, repeated stimulation at the same point in the mesencephalon and with the same intensity, evoked progressively greater increases of blood flow. The effect of eserine, it will be noted, came comparatively slowly. Eight minutes after completion of the injection—the eserine was administered intravenously, diluted in 5 cc of 0.9 per cent saline, during the course of about one minute—the response to stimulation was an increase of 130 per cent, and after 17 minutes it amounted to 260 per cent. Even the blood pressure response to stimulation showed a marked change. At the start of the experiment a minor rise of blood pressure occurred; but as the eserine exerted its effect, so did this rise change to a fairly substantial fall of blood pressure as a result of the pronounced decrease in peripheral resistance. In considering the fact that this latter decrease, in the skeletal muscles, was so conspicuously reflected in the blood pressure response, it must also be borne in mind that the weak intensity of stimulation probably did not excite any major number of vasoconstrictor neurons to other vascular areas. In this way the muscular vasodilatation came to be the predominant component of the response pattern. The dose of atropine—0.2 mg per kg—that usually sufficed to block the vasodilatation completely, in this experiment had a reducing effect only about one-tenth of that it would have shown in a non-eserinized animal. Not until the cat had received a total of 1.0 mg atropine per kg was the vasodilatation virtually blocked.

Note the potentiating effect of eserine and the large doses of atropine necessary for abolishing the vasodilator responses.

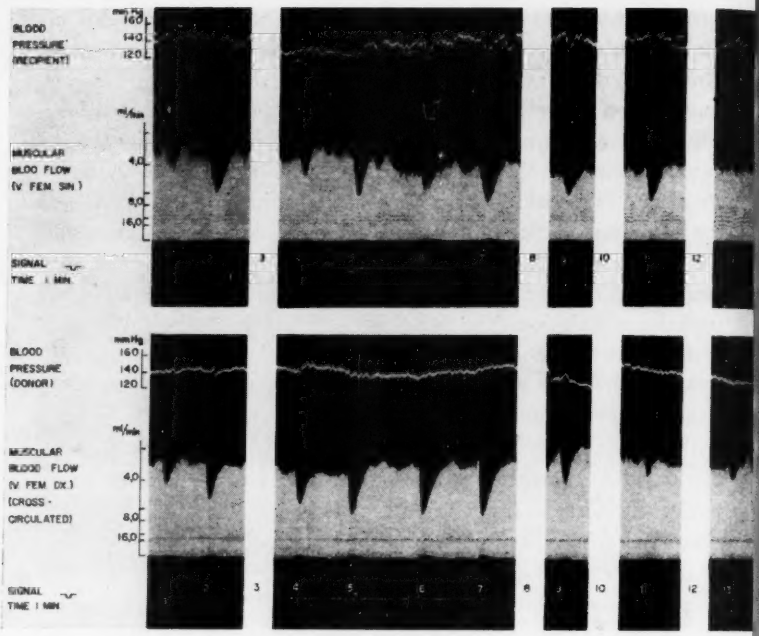


Fig. 23. Cross-circulation.

Recipient cat 3.3 kg. Dial 50 mg/kg. Aa. carotides commun. occluded.

Donor cat 3.0 kg. Dial 50 mg/kg. A. carotis commun. sin. occluded.

Vasodilator responses in the muscles of the left (not cross-circulated) and right (cross-circulated) hind legs. Effect of eserine on the vasodilator responses in the cross-circulated leg.

1. Stim., 1.5 V, 15 sec. Increase of flow, left 30 %, right 30 %
2. „ 2.0 „ „ „ „ „ „ „ 60 %, „ 60 %
3. Eserine 0.1 mg/kg I.V. to the donor.
4. Stim., 1.5 V, 15 sec. Increase of flow, left 30 %, right 50 %
5. „ 2.0 „ „ „ „ „ „ „ 70 %, „ 90 %
6. „ 1.5 „ „ „ „ „ „ „ 30 %, „ 100 %
7. „ 2.0 „ „ „ „ „ „ „ 70 %, „ 110 %
8. Atropine 0.3 mg/kg I.V. to the donor.
9. Stim., 1.5 V, 15 sec. Increase of flow, left 30 %, right 40 %
10. Atropine 0.5 mg/kg I.V. to the donor.
11. Stim., 2.0 V, 15 sec. Increase of flow, left 60 %, right < 20 %
12. Atropine 0.2 mg/kg I.V. to the recipient.
13. Stim., 2.0 V, 15 sec. Increase of flow, left , right < 20 %

Note the potentiated vasodilator responses in the cross-circulated leg compared to those in the other leg.

In order to throw further light on the potentiating effect of this anticholinesterase, eserine, cross-circulation experiments were conducted with the aim of studying the peripheral effect directly (figure 23). The same type of cross-circulation technique was used as that in studies of the peripheral effect of atropine. Numbers 1 and 2 in figure 23 show vasodilatation in the skeletal muscles of the two hind legs, the right one perfused by blood from the donor cat. Two different intensities of stimuli were used—1.5 and 2.0 volts respectively. After administration of eserine in the donor animal, further stimulation elicited mounting increases of blood flow in the right leg. The responses in the left leg, which was not cross-circulated, were virtually unchanged. The increase of flow in the right leg before eserine was about 30 per cent (1 in figure 23) at a stimulation intensity of 1.5 volts; under the full action of eserine it amounted to 100 per cent, or in other words was trebled. The corresponding figures at a stimulation intensity of 2.0 volts were 60 and 110 per cent respectively. A plausible reason why the response in this case was only doubled is that at the higher intensity more vasodilator neurons were activated and the post-ganglionic fibers were caused to fire more frequently (see section 2), so that a relatively large part of the dilatation capacity of the vascular area was already utilized before eserinization. At the higher stimulation intensity it was difficult with atropine to block the vasodilatation completely. After administration of 1.0 mg atropine per kg in the donor animal, a slight increase of flow persisted (11 in figure 23). In the intact left leg, on the other hand, the corresponding response was totally blocked by 0.2 mg atropine per kg.

Comment

Atropine is known to have a blocking action on the muscarine-like effects of acetylcholine. This circumstance has often played a major role in discussion of the transmitter substance at autonomic nerve endings. If atropine has been capable of blocking the effects produced by activity in such nerves, it has been taken as evidence of a cholinergic transmission. Yet the problem complex of atropine block of cholinergic transmission is somewhat

intricate, for autonomic effects have also been described in which other factors have strongly suggested a cholinergic transmission but which have not been influenced by atropine. Thus the chorda tympani and the lingual nerve are considered to have vasodilator fibers of cholinergic type to the tongue; for electrical stimulation elicits considerable vasodilatation in the tongue and the appearance of acetylcholine in venous blood or perfusate (FELDBERG, 1933). The responses cannot be blocked by atropine (also verified by ERICI and UVNÄS, 1952).

The sympathetic vasodilator nerves are today thought to be exclusively cholinergic, and in general their effects can be blocked by atropine. However, under some conditions—if the experimental animal has received Dibenamine as a sympatholytic—atropine has this effect only in some cases (FOLKOW, HAEGER and UVNÄS, 1948; FOLKOW and UVNÄS, 1950). Other sympatholytics, such as Dihydroergotamine, do not influence the atropine block. This phenomenon still remains to be elucidated.

We thus arrive at the following conclusions: No other transmission mechanism at autonomic nerve terminals is known, than the cholinergic one which is blocked by atropine; but there exists a cholinergic transmission at autonomic nerve endings which is not blocked by atropine.

The observed vasodilatation evoked in skeletal muscles by mesencephalic stimulation could virtually always be blocked with atropine. Cross-circulation experiments showed the action of atropine to be peripheral. This finding alone should thus warrant the conslusion that the peripheral transmission of the activated sympathetic vasodilator fibers was cholinergic.

As mentioned above, it has long been known that vasodilatation resulting from peripheral stimulation of sympathetic vasodilator nerves could be potentiated by eserine, which inhibits the enzymatic breakdown of acetylcholine (ROSENBLUETH and CANNON, 1935; FOLKOW, HAEGER and UVNÄS, 1948). It is not surprising, therefore, that the same results have been obtained in activation of such nerves by stimulation of central structures—this had never before been demonstrated.

In order to show the cholinergic transmission more directly, attempts might have been made in perfusion experiments to demonstrate acetylcholine in perfusate from skeletal muscles during mesencephalic stimulation. However, no such experiments were conducted, partly due to the difficulty of increasing the duration of the responses by raising that of stimulation above 10-20 seconds (see section 2).

8. Action of a Sympatholytic Drug on the Vasodilator Responses in the Muscles and on the Vasoconstrictor Responses in the Skin

Sympatholytic drugs have often been used for demonstrating the increase of blood flow in skeletal muscles on stimulation of the sympathetic vasomotor outflow, e.g. the abdominal sympathetic chain. For in such stimulation both vasoconstrictor and vasodilator fibers are activated, the effect of the former usually predominating, unless a special stimulation technique is employed. If a sympatholytic is administered to the animal, the effect of vasoconstrictor impulses will be reduced or blocked and that of the vasodilator impulses will then produce an increase of blood flow (e.g. DALE, 1913; ROSENBLUETH and CANNON, 1935; BÜLBRING and BURN, 1935). For sympatholytics of ergotamine type block an adrenergic transmission mechanism but do not affect a cholinergic one.

Having regard to the complex vasomotor response pattern in mesencephalic stimulation of the type described here, it was worth while studying what effect a sympatholytic might have on that pattern and its various components. Dihydroergotamine was chosen as the sympatholytic, since it is one of the least toxic. A contributory reason for this choice was the observation that some sympatholytics, such as ergotamine and Dibenamine, in some way influence the blocking effect of atropine on sympathetic vasodilator responses, whereas Dihydroergotamine does not have that property (FOLKOW, HAEGER and UVNÄS, 1948; FOLKOW and

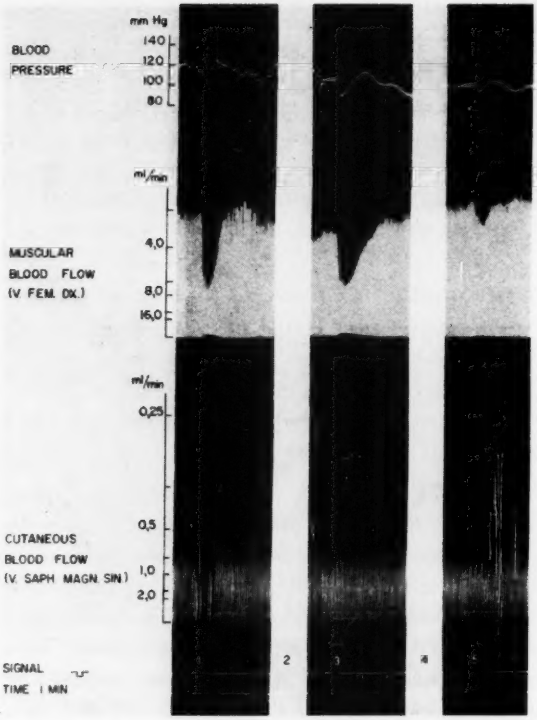


Fig. 24. Cat 2.2 kg. Dial 50 mg/kg.
Vasodilator responses in the muscles of the right hind leg and vasoconstrictor responses in the skin of the left hind leg to stimulation in the right part of the tectum mesencephali before and after Dihydroergotamine.

1. Stimulation, 2.5 V, 15 sec.
2. Dihydroergotamine 0.5 mg/kg I.V.
3. Stimulation, 2.5 V, 15 sec.
4. Atropine 0.1 mg/kg I.V.
5. Stimulation, 2.5 V, 20 sec.

Note the disappearance of vasoconstrictor response in the skin after Dihydroergotamine. The vasodilator responses in the muscles are uninfluenced.

Uvnäs, 1950). Figure 24 shows an experiment of this kind. From the right hind leg the muscle blood flow was recorded in the femoral vein; from the left, the cutaneous blood flow in the long saphenous vein. Mesencephalic stimulation was done in the usual way and produced the usual responses consisting of vasodilatation in the muscles and vasoconstriction in the skin (1 in figure 24).

The blood pressure response consisted of a minor, though fully distinct rise. After Dihydroergotamine 0.5 mg per kg, administered intravenously during the course of a few minutes, the response pattern was changed. The cutaneous vasoconstriction was quite absent but the vasodilatation in the muscles persisted. The magnitude of the increase of flow was unchanged, but after stimulation had ceased there was a somewhat longer interval before the blood flow returned to its initial level. As a sign of the absence of vasoconstriction there was an abrupt fall of blood pressure amounting to 20-30 mm Hg, or as great as the earlier rise. The dose of Dihydroergotamine used did not influence the effect of atropine, of which 0.2 mg per kg almost totally blocked the vasodilatation.

The effect of Dihydroergotamine on the intestinal vasoconstrictions was not studied, but probably those too were blocked. For instance, the fall of blood pressure on stimulation after Dihydroergotamine in the reported experiment suggested that all vasoconstrictor effects were abolished.

Comment

The action of sympatholytic ergot drugs on the circulatory apparatus is exceedingly complex. Since these substances have several different effects, their action on vasomotor responses is often difficult to elucidate. In the first place they produce a central effect: reduction of the activity of the vasomotor center with blocking of various reflexes, as for instance baroceptor ones. Secondly, they have a sympathoadrenolytic effect; and thirdly, they exert a direct contracting effect on the smooth muscle of the vascular walls (*vide* e.g. ROTHLIN, 1946, 1947; GUGGISBERG, 1954).

Stimulation of, for example, the abdominal sympathetic in an ergotized animal (dog or cat) produces, as mentioned in the foregoing, an increase of the blood flow in the hind legs, due to blocking of the effect of the vasoconstrictor impulses but not of the vasodilator ones. The results of this investigation show that even central activation of sympathetic vasodilator nerves in an animal given Dihydroergotamine induced an increase of flow.

However, coincident stimulation of vasoconstrictor neurons did not give rise to any decrease of flow. The exact localization of the blocking action of the drug in this case is not fully clear. It may be central, either in the stimulated mesencephalic structure or in more caudal parts of the brain stem and spinal medulla. It may also be peripheral, of sympatholytic type. Probably, both mechanisms have an influence. Dihydroergotamine is known to have a pronounced sympatholytic effect, and the dose employed is sufficient to block the adrenergic transmission mechanism in peripheral stimulation of the sympathetic outflow (LINDGREN and UVNÄS, unpublished observations).

9. The Role of the Adrenals in the Vascular Reaction Pattern

Extirpation or denervation of the adrenals was done in a number of the experiments described in the foregoing. Such measures precluded the possibility of the observed responses being due to, or influenced by, adrenal medullary hormones. If, however, it is desired to elucidate this possible component of the reaction pattern, several modes of approach are available. In this investigation the possible presence of secreted hormones was studied on the basis of phenomena within the experimental animal itself. One advantage of this mode of procedure is that the responses can be read immediately.

It is mainly the following factors that may conceivably influence the blood flow in a vascular area deprived of its vasomotor innervation: (1) The intrinsic vascular tone; (2) mechanical factors such as muscular movements; (3) arterial blood pressure; (4) the venous pressure; (5) local humoral factors such as various metabolites; and (6) blood-borne vaso-active substances. Several of these factors are probably either fairly constant (intrinsic vascular tone, local metabolites) during a short phase of an acute experiment, or can be recorded or observed, and hence checked (blood pressure, venous pressure, and muscular movements). Blood-borne vaso-active substances may be of varying origin:

they could be hormones from the adrenal medulla, or circulating transmitter substances from peripheral nerve terminals notably of the autonomic system. This lastnamed possibility was specially studied by CANNON and his associates (for references, see the monographs by CANNON and ROSENBLUETH, 1937 and 1949). However, in the opinion of many authors, such remote effects seldom occur under physiologic conditions, and when they do so they are of quite negligible magnitude compared with other sympathetic effector mechanisms (*vide* CELANDER, 1954). The principal source accordingly seems to be the adrenal medulla.

A characteristic of blood vessels deprived of their vasomotor innervation is the supersensitivity to various drugs that develops after a short time. This phenomenon is of fundamental importance in the present study of the adrenal medullary activity, for the amount of catechols produced in activation of the adrenals within the physiologic range has only a minor influence on normal vessels. Denervated vessels react not only with constriction to smaller than normal doses of adrenaline and noradrenaline, but also with dilatation to several substances (e.g. adrenaline and acetylcholine) that normally have that effect.

Several workers have made use of tissue deprived of its autonomic innervation for studying adrenal responses and other active humoral substances (*vide* CANNON and ROSENBLUETH, 1949). In this investigation the responses were studied both in the blood flow through the muscles of a sympathectomized hind leg and in that through a fore paw which had been deprived of its somatic and autonomic innervation. The aseptic operations were performed a week or two before the acute experiment.

Responses in Muscle Vessels Deprived of their Sympathetic Innervation

In the foregoing have been described experiments on unilaterally sympathectomized animals where the blood flow was recorded coincidently on the sympathectomized and the intact side. In these experiments mesencephalic stimulation caused no demonstrable change of blood flow in the sympathectomized leg; only the usual vasodilatation appeared in the intact leg. It should

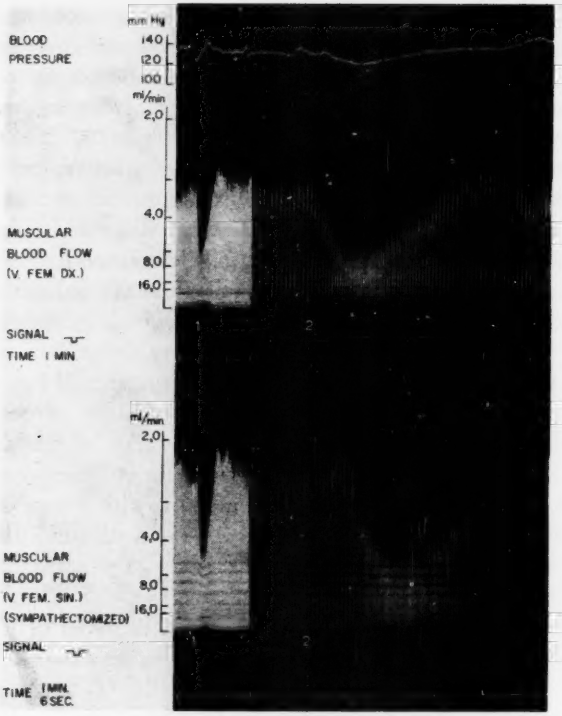


Fig. 25. Cat 2.0 kg. Dial 40 mg/kg.
Left hind leg sympathectomized 14 days before the experiment.
A. carotis commun. sin. occluded.
Vasodilator responses in the muscles of the right and left hind legs to stimulation in the right part of the tectum mesencephali.
1. Stimulation, 2.5 V, 10 sec.
2. „ — „ „ „ „ „
Note the difference in latency between the normal and the sympathectomized leg. (The adrenals were intact.)

be observed, however, that in these experiments the adrenals had already been eliminated at the outset.

In similar experiments, though with intact adrenals, there was sometimes an increase of flow even in the muscles of the sympathectomized leg. This occurred fairly regularly when stimuli of high intensity were used. The increase of flow could be

quite considerable and, superficially, appeared to have the same character as that due to activity in cholinergic sympathetic vasodilator fibers. However, a more detailed analysis disclosed several differences. For instance, there was a striking difference in latency between the increases of flow in the intact and the sympathectomized leg. An experiment in which this detail was especially studied is illustrated in figure 25. Mesencephalic stimulation produced outwardly (1 in figure 25) similar effects in the two legs, the increases of flow being of approximately the same magnitude. But when the speed of the kymograph was increased tenfold, so that the course could be studied in greater detail and each drop interval read, a distinct difference in latency emerged. In the intact leg the blood flow commenced to increase 6-7 seconds after the start of stimulation, but in the sympathectomized leg the corresponding time was 16-18 seconds. The difference thus amounted to about 10 seconds. In view of this discrepancy in latency the vasodilatation in the sympathectomized leg is not likely to have been produced directly by nervous means; it is more plausible to attribute it to some humoral factor.

Another fundamental circumstance which in itself shows that the increase of flow in a sympathectomized leg differs essentially from that effected via cholinergic sympathetic vasodilator nerves, is the influence of atropine. This substance did not affect the response in the vasomotor denervated leg (figure 26), at all events in the doses tried; i.e., those which had been found quite sufficient to block the usual vasodilatation in intact muscles. On the contrary, the increase of flow appeared to be somewhat greater after atropine—at least in the experiment illustrated. In the present instance this was probably due, however, to the difference in blood pressure response to stimulation before and after atropine. The blood pressure showed a minimum of 110 mm Hg during stimulation in the former case, and a maximum of 140 mm Hg in the latter.

There is, accordingly, much to suggest that the increase of flow in the muscles of a sympathectomized leg which attends activation of sympathetic cholinergic vasodilator nerves is due to adrenal medullary activity. It has been pointed out elsewhere that such an increase of flow did not occur in a sympathectomized

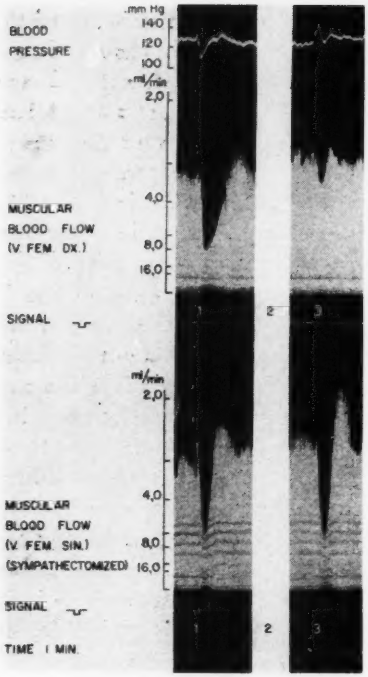


Fig. 26. Cat 2.0 kg. Dial 40 mg/kg.
Left hind leg sympathectomized 14 days before the experiment.
A. carotis commun. sin. occluded.
Vasodilator responses in the muscles of the right and left hind legs to stimulation in the right part of the tectum mesencephali before and after atropine.
1. Stimulation, 2.5 V, 10 sec.
2. Atropine 0.2 mg/kg I.V.
3. Stimulation, 2.5 V, 10 sec.
Note that the vasodilatation in the sympathectomized leg is unchanged after atropine. (Intact adrenals.)

leg if the adrenals had been eliminated. This does not, of course, demonstrate conclusively that the adrenals are involved in the mechanism described here; it may be objected, for instance, that activation of sympathetic vasodilator nerves without a coincident increase of flow in the sympathectomized leg was occasionally observed also in animals with intact adrenals. Far weightier

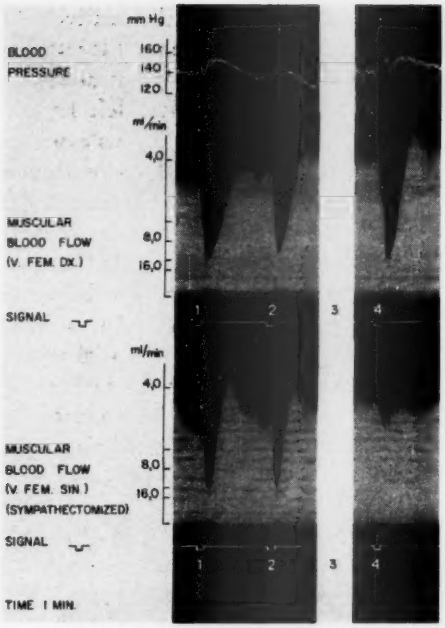


Fig. 27. Cat 3.5 kg. Dial 50 mg/kg.
Left hind leg sympathectomized 27 days before the experiment.
A. carotis commun. sin. occluded.
Vasodilator responses in the muscles of the right and left hind legs to stimulation in the left part of the tectum mesencephali.

1. Stimulation, 3.5 V, 15 sec.
2. „ — „ „ „ „ „
3. Both adrenals eliminated.
4. Stimulation, 3.5 V, 15 sec.

Note the disappearance of the vasodilator responses in the sympathectomized leg on stimulation after elimination of the adrenals.

evidence as to the role of the adrenals is provided by an experiment in which the adrenal function was eliminated during the course of the experiment, so that observations could be made both before and after such elimination. An experiment of this kind is illustrated in figure 27. The cat had been sympathectomized on the left side 27 days before the experiment, by excision of the abdominal portion of the left sympathetic chain. The blood flow in the muscles of both hind legs was recorded in the usual

way. Mesencephalic stimulation had the relatively high intensity of 3.5 volts. The vasodilatation in the right leg was commensurate thereto and may doubtless be regarded as almost maximal. An increase of blood flow appeared in the left leg too, though of somewhat lesser extent. At the outset of this experiment preparations had been made for eliminating the adrenals as conveniently as possible during the course of the experiment. This was done here by ligation of all nervous and vascular connections to and from the relevant organs (3 in figure 27). Further stimulation activated sympathetic vasodilator nerves as before and produced a marked increase of flow in the right leg. In the left leg, however, the only vasodilatation found was a very slight one secondary to the rise of blood pressure. Evidently the earlier response in the vasomotor denervated left leg had been caused by an abrupt increase of the secretion of adrenal catechols as a result of the stimulation.

Responses in Cutaneous Vessels Deprived of their Sympathetic Innervation

The adrenal activation, as pointed out above, was also studied on the basis of the vascular responses in a totally denervated fore paw. This blood flow—measured in the cephalic vein—came chiefly from cutaneous tissue. Since the adrenals were of interest only with respect to the degree and type of activation that coincided with activation of sympathetic cholinergic vasodilator fibers to the skeletal muscles, this type of experiment was complicated by the fact that three different blood flows had to be recorded concurrently. The muscle blood flow was observed as a check that the cerebral stimulation activated sympathetic vasodilator fibers; the changes in cutaneous blood flow from a region with intact innervation were studied for comparison with those in the denervated area of skin.

Figure 28 shows the results of such an experiment. By cutting the nerves from the brachial plexus to the right foreleg, the latter had been almost totally denervated 19 days before the acute experiment. The muscle blood flow was recorded, as usual, in the right femoral vein. In addition the blood flow was recorded

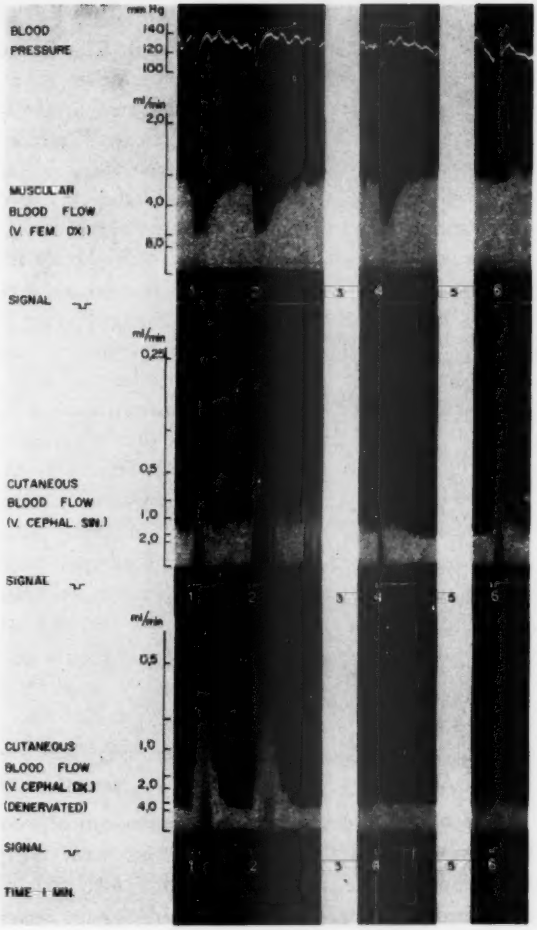


Fig. 28. Cat 4.1 kg. Dial 60 mg/kg.
Right foreleg denervated 19 days before the experiment.
Aa. carotides commun. occluded. Nn. vagi cut.

Vasodilator responses in the muscles of the right hind leg and vasoconstrictor responses in the skin of the left and right forelegs to stimulation in the right part of the tectum mesencephali.

1. Stimulation, 3.0 V, 10 sec.
2. „ — „ „ „ „ „
3. Both adrenals removed.
4. Stimulation, 3.0 V, 10 sec.
5. Atropine 0.3 mg/kg I.V.
6. Stimulation, 3.0 V, 10 sec.

Note the disappearance of vasoconstriction in the denervated left foreleg after removal of the adrenals.

in two cutaneous zones—the fore paws. At 1 and 2 in figure 28, a point in the mesencephalon was stimulated. The responses in the three vascular sectors studied were as follows. The muscle blood flow increased substantially, and in the two cutaneous areas there was a pronounced decrease of blood flow. The blood pressure response was not uniform—first a rise, then a fall. The character of the vasoconstriction differed in the two fore paws. The latency cannot be read from the relevant curve, but a difference was observed: the latency was about 10 seconds longer in the denervated left leg. Moreover, the vasoconstriction persisted longer in that leg. The response pattern changed after bilateral adrenalectomy. The vasodilatation in the muscles remained unchanged in character but was perhaps somewhat less than before. In the denervated leg the substantial vasoconstriction had disappeared; the minimal variations of flow that occurred may be explained as passive to the changes of blood pressure. In the intact leg the vasoconstriction persisted, though it was of somewhat less extent. Evidently the nervous component of this reaction had previously been supported by the humoral adrenal component. After 0.2 mg atropine per kg, only the vasoconstriction in the innervated cutaneous sector persisted of the original responses. The blood pressure response in this case was purely of pressor type.

Effect of Adrenaline and Noradrenaline on Muscle and Cutaneous Vessels Deprived of their Sympathetic Innervation

The results of the aforegoing experiments indicate only that the adrenals may be activated coincidently with sympathetic vasodilator fibers to skeletal muscles and vasoconstrictor fibers to the skin (and splanchnic area) on stimulation in certain parts of the mesencephalon. They do not show the degree of adrenal activation, nor the nature of the substance or substances discharged into the blood stream. As is well known, the vaso-active substances in the adrenal medullary secretion are adrenaline and noradrenaline. Their relative proportions may, however, vary widely, depending on the mode of activation of the adrenal medulla; and quite recently FOLKOW and EULER (1954) reported

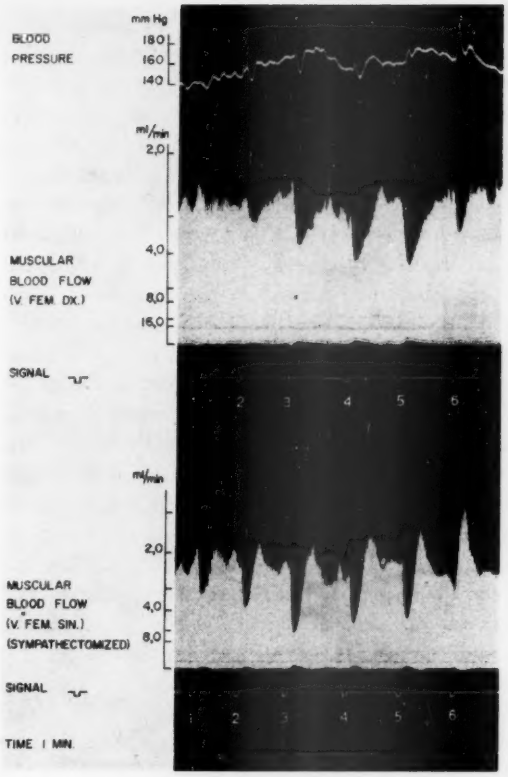


Fig. 29. Cat 3.3 kg. Dial 50 mg/kg.
Left hind leg sympathectomized 13 days before the experiment.
Adrenals removed. A. carotis commun. sin. occluded.
Vasodilator and vasoconstrictor responses in the muscles of the right and left hind legs to intravenous injections of adrenaline.

1. Adrenaline	0.1	μg.	4. Adrenaline	1	μg.
2. „	0.25	„	5. „	5	„
3. „	0.5	„	6. „	10	„

Note the greater effect of adrenaline in the sympathectomized leg.

an investigation in which they showed that in stimulation of various points in the feline hypothalamus the adrenal medullary secretion sometimes contained only one of the substances.

In order to elucidate the reactions to adrenaline and noradrenaline of the denervated vessels in muscles and skin, a series of experiments was conducted in which the sensitivity to those substances was studied. Varying amounts of them were injected intravenously, diluted in, usually, 0.2 ml saline, during the course of about 10 seconds. The blood flow was recorded both in a vasomotor denervated vascular area and, for comparative purposes, in the intact contralateral vascular zone. The muscle blood flow was studied in both hind legs of unilaterally sympathectomized cats; the cutaneous blood flow in the fore paws, one of which had been denervated. The results of such an experiment are shown in figures 29 and 30. The animal had been sympathectomized on the left side 13 days before the experiment. In figure 29, adrenaline was injected in increasing doses into the left cephalic vein. In the doses employed, it usually produced chiefly dilatation of muscle vessels. A fairly great difference in sensitivity will be noted between the two vascular areas. In the sympathectomized leg there was already an increase of flow at 0.10 μg and 0.25 μg adrenaline, which small doses did not affect the flow in the intact leg, nor the blood pressure either. At 0.5 μg adrenaline the vasodilatation was maximal in the left leg; but in the right leg 5 μg was required to produce maximum vasodilatation. The latency of the observed increases of flow is not evident from the curves, but was measured at about 20 seconds; i.e., the same order of magnitude as that observed for the increase of flow in sympathectomized muscles following adrenal medullary activation by mesencephalic stimulation. It will be noted, too, that the vessels in the sympathectomized leg were more sensitive with regard to both the vasodilator and the vasoconstrictor properties of adrenaline. For instance, 10 μg induced clear-cut vasoconstriction in that leg, whereas vasodilatation was predominant in the other. From this and a few similar experiments it may be concluded that sympathectomy had increased five- to ten-fold the sensitivity of the muscle vessels.

The muscle vessels reacted only with constriction to intravenous injections of noradrenaline (figure 30; the same animal as in figure 29). The sensitivity to this substance was increased in about the same degree as that to adrenaline. However, the relative insen-

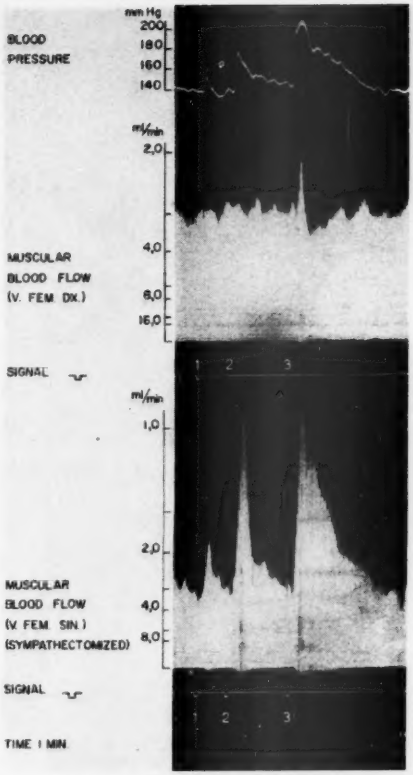


Fig. 30. Cat 3.3 kg. Dial 50 mg/kg.
Left hind leg sympathectomized 13 days before the experiment.
Adrenals removed. A. carotis commun. sin. occluded.
Vasoconstrictor responses in the muscles of the right and left hind legs to intravenous injections of noradrenaline.

1. Noradrenaline 1 μg.
2. „ — „ 5 „
3. „ — „ 10 „

Note the greater effect of noradrenaline in the sympathectomized leg.

sitivity of the muscle vessels on both the denervated and the intact side was noticeable; only after fairly large doses did a decrease of flow appear. However, it should be borne in mind,

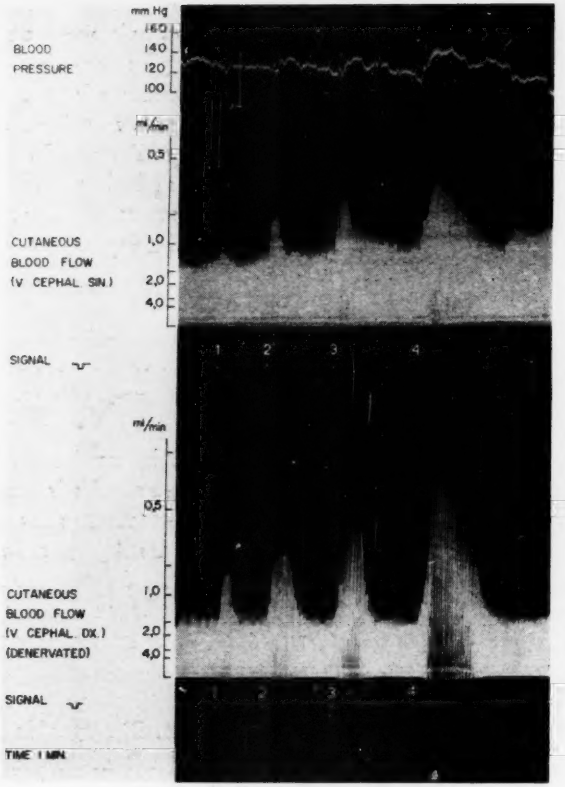


Fig. 31. Cat 4.2 kg. Dial 50 mg/kg.
Right foreleg denervated 26 days before the experiment.
A. carotis commun. sin. occluded. Nn. vagi cut.
Vasoconstrictor responses in the skin of the left and right forelegs to intravenous injections of adrenaline.

1. Adrenaline 0.1 μg. 3. Adrenaline 1 μg.
2. „ — „ 0.5 „ 4. „ — „ 10 „

Note the greater effect of adrenaline in the denervated leg.

in this connection, that with the technique employed the substantial rises of blood pressure greatly influenced the blood flow and reduced its decreases.

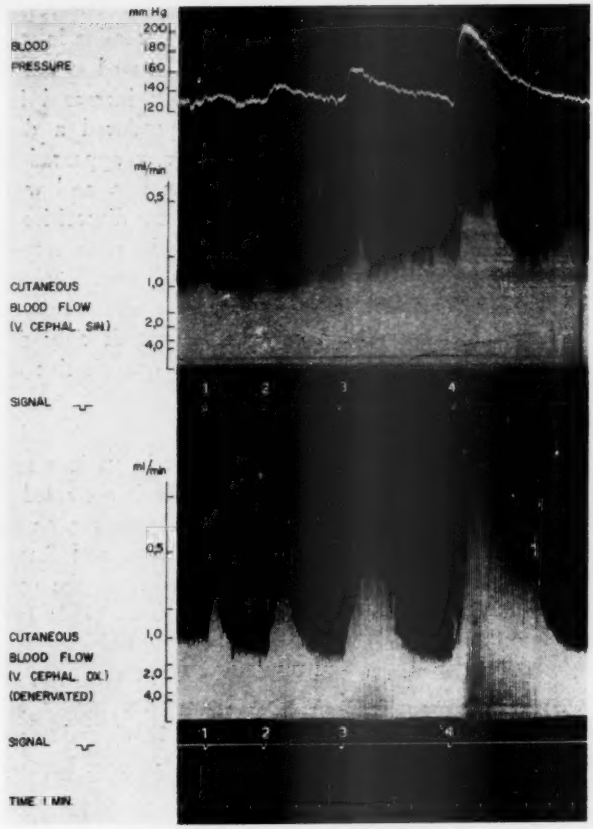


Fig. 32. Cat 4.2 kg. Dial 50 mg/kg.
Right foreleg denervated 26 days before the experiment.
A. carotis commun. sin. occluded. Nn. vagi cut.
Vasoconstrictor responses in the skin of the left and right forelegs to intravenous injections of noradrenaline.
1. Noradrenaline 0.1 μg. 3. Noradrenaline 1 μg.
2. „ — „ 0.5 „ 4. „ — „ 10 „
Note the greater effect of noradrenaline in the denervated leg.

The supersensitivity of the cutaneous vessels following denervation was studied in experiments of similar type. The blood flow was recorded from the two fore paws, one of which had been

denervated a few weeks before the experiments. The results of intravenous injection of adrenaline and noradrenaline in varying doses are shown in figures 31 and 32. With regard to cutaneous vessels, too, the sensitivity was considerably increased in the denervated leg, where doses of 0.1-1 μg produced a distinct decrease of flow. The difference in sensitivity appeared to be particularly marked in the case of noradrenaline, and was less for adrenaline. However, there were fairly great disparities in the dose-response relationship in different animals, with respect to both muscular and cutaneous areas; but the difference in sensitivity between denervated and intact vascular areas was usually more or less unchanged. Hence the experiments permit only of circumspect conclusions regarding the absolute quantitative conditions.

Comment

Numerous investigations have shown that in various reflexes or in central stimulation the adrenal medulla is activated coincidently with generalized vasoconstrictor discharge, e.g. on stimulation of a peripheral afferent nerve (CANNON and RAPPORT, 1921; EULER and FOLKOW, 1953), on occlusion of the carotids (KAINDL and EULER, 1951; EULER and FOLKOW, 1953; HOLTZ, ENGELHARDT, GREEFF and SCHÜMANN, 1952), on asphyxia (RAPELA and HOUSSAY, 1952; EULER and FOLKOW, 1953; CELANDER, 1954), on electrical stimulation of the vasoconstrictor center in the medulla oblongata (CHEN, LIM, WANG and YI, 1936), and on electrical stimulation in the hypothalamus (HOUSSAY and MOLINELLI, 1925; MAGOUN, RANSON and HETHERINGTON, 1937; BRÜCKE, LOUDON and WERNER, 1951; BRAUNER, BRÜCKE, KAINDL and NEUMAYR, 1951; BRÜCKE, KAINDL and MAYER, 1952; FOLKOW and EULER, 1954).

With the results presented here it has been shown that the adrenal medulla may be activated concurrently with sympathetic vasodilator nerves, on topical stimulation in the mesencephalon.

It emerged that the adrenal medulla generally was not activated until the stimulation had a higher intensity than that normally required for activation of the vasomotor nerves. It may be debated whether this finding implies that the neurons referable to the central outflow to the adrenals had a higher threshold

than others, or whether the experimental procedure permitted the recording only of high adrenal activity. The method of studying the influence of adrenal catechols on a denervated hypersensitive vascular area was found to have a sensitivity of about 0.1 μg in a single intravenous injection with an injection time of approximately 10 seconds. CELANDER (1954) reported that in cats the maximal catechol secretion associated with direct splanchnic stimulation amounted to about 5 μg per kg per minute. He said of this value: "*It rather represents the theoretical average upper limit of catechol secretion in the cat which will probably never be reached during any type of reflex activation of the adrenal medullae in the living body.*" The amounts measured in various types of reflex activation are, moreover, considerably lower, generally not exceeding 1-2 μg per kg per minute. This means that the anticipated maximal amount of catechols exceeded clearly though not greatly the limit of the relevant method's sensitivity.

Although the results obtained in the present investigation were not subjected to strictly quantitative analysis, the catechol secretion may be estimated to have been of the same order of magnitude as that in physiologically occurring activation of the adrenal medulla.

It seems clear, however, that the amounts secreted were generally too small to have any appreciable influence on the blood flow in normally innervated vascular areas. It is evident from the preceding section, moreover, that the observed reactions in those areas were almost wholly referable to the direct vasomotor innervation. This is also consistent with CELANDER's observations (1954) that the adrenals play, quantitatively, a minor role compared with the vasomotor nerves in the control of vascular tone under varying physiologic conditions. Further, it may explain why ELIASSON, FOLKOW, LINDGREN and UVNÄS (1951), for instance, did not observe any adrenal medullary activation in hypothalamic stimulation designed to activate the sympathetic vasodilator outflow. Whether these two sympathetic components may be activated coincidently in hypothalamic stimulation is not known, however; but having regard to the results of this investigation, it seems likely.

It will be seen that adrenaline in small doses had a purely dilator effect on the muscle vessels, but in no case did noradrenaline have a similar effect, regardless of dose. Mesencephalic stimulation too produced vasodilatation in the sympathectomized muscular area. The conclusion may thus be drawn that the adrenal medullary secretion invariably contained some adrenaline. It is difficult, on the other hand, to draw any conclusions about the relative proportions of adrenaline and noradrenaline. The effects on both muscle and cutaneous vessels might be attributed to adrenaline alone, but a substantial content of noradrenaline may have been present too; for due to the relative insensitivity of muscle vessels to noradrenaline the effect of adrenaline predominates here. On innervated muscle vessels this effect is still pronounced with a mixture containing up to 75 per cent noradrenaline (LARGY, GREENFIELD, MCCORRY and WHELAN, 1950).

Unfortunately, no determination was possible of the relative proportions of adrenaline and noradrenaline. FOLKOW and EULER (1954), using stimulation in the feline brain stem, obtained adrenal responses that sometimes consisted chiefly of adrenaline, sometimes chiefly of noradrenaline. A study of figure 1 (semischematic drawing of the localization of stimulated points) in their paper shows that the points located in the mesencephalon closest to the aqueductus Sylvii—i.e., adjacent to the area where stimulation was mostly applied in the present investigation—had been associated with a predominantly adrenaline secretion.

Discussion

The aim of the experiments described in this chapter was to study the peripheral vascular responses to electrical stimulation in the mesencephalon in those cases where one feature of them was vasodilatation in the skeletal muscles.

Various reasons can be adduced for choosing the muscles of the extremities, a paw and an intestinal area for the study of these peripheral responses. For instance, these areas have differing

vasomotor innervations. The skeletal muscles in the cat have a double vasomotor innervation: both sympathetic vasoconstrictor fibers and sympathetic vasodilator fibers. The paw largely consists of cutaneous tissue and has only a sympathetic vasoconstrictor innervation. The postganglionic fibers are principally distributed via the peripheral nerves. With respect to innervation, an intestinal sector belongs to what is usually termed the splanchnic area, which only has an autonomic innervation. The sympathetic vasoconstrictor nerves are distributed from the celiac ganglion and the superior and inferior mesenteric ganglia. These tissues, the skeletal muscles, skin and splanchnic region, together represent the greater part of the peripheral circulation.

Most of the early workers who investigated the mesencephalon were content to observe the influence of that region on the circulatory apparatus, without studying the peripheral responses lying behind the blood pressure reactions. Their investigations are, therefore, somewhat irrelevant to the observations reported here, which are largely concerned with the peripheral mechanism of the reactions.

The reaction pattern elicited, in the present experiments, by electrical stimulation in the mesencephalon, may be regarded as systemic effects of partial type in the sense that some portions of the sympathetic efferent system were involved throughout the organism, but others did not appear to be involved. The vasomotor effects, as pointed out, consisted of vasodilator activation to skeletal muscles and vasoconstrictor activation to skin and intestines. Moreover, there was activation of the adrenal medulla with secretion of catechols. The muscular vasodilatation as well as the cutaneous vasoconstriction occurred in both the fore and the hind limbs. The effects were also bilateral. Accordingly, no differentiated localization for different parts of the body was detectable; rather, generalized effects were the rule. However, the method employed may be regarded as somewhat rough, with regard to both the stimulation and the recording technique; and the stimulation probably activated a fairly large number of neurons concurrently.

There should be no doubt that the observed vasomotor reactions were of the same character as those described by ELIASSON,

Folkow, Lindgren and Uvnäs (1951) in stimulation in the anterior hypothalamus. Aside from the observation of adrenal medullary activation the reaction patterns coincide, both with regard to activation of vasodilator and of vasoconstrictor nerves, and with respect to the distribution of the responses. The only plausible explanation seems to be that the relevant mesencephalic structures constitute a part of the efferent outflow of the neuron system. These problems will be treated further, however, in Chapters III and IV.

There are, nevertheless, several factors which suggest that the hypothalamus does not constitute the highest central representation of this neuron system. Eliasson, Lindgren and Uvnäs (1952) found, in dogs, that the sympathetic vasodilator nerves whose effect could be blocked with atropine were activated by electrical stimulation in the motor cortex. They did not, however, investigate any possible coincident responses in other tissues.

With different recording techniques, plethysmography and organ volume determinations, other workers have obtained complex vasomotor reactions with patterns resembling those found in the present investigation. Thus Weber (1906) observed that electrical stimulation in the premotor cortex of curarized dogs and cats produced a rise in blood pressure and increase in volume of the extremities coincidently with a decrease in the intestinal volume. After section of the splanchnic nerves the increase of volume persisted in the extremities but there was still a rise of blood pressure, albeit considerably less. Weber wrote: "*Ob die noch zurückbleibende geringe Blutdrucksteigerung bei Rindenreizung nach Durchschneidung der Splanchnici durch Kontraktion der verhältnismässig wenigen Blutgefässe der Bauchorgane, die von andern Nerven versorgt werden, verursacht wird, oder ob noch andere Umstände mitwirken, blieb vorläufig unaufgeklärt.*" It is possible that the persisting vasoconstriction occurred in the skin and that the muscles were the site of the vasodilatation.

Green and Hoff (1937) studied similar peripheral responses to stimulation of the gyrus sigmoideus in cats. They found vasodilatation in the extremities (bilateral effects) and coincident vasoconstriction in the kidneys. Since this vasodilatation also

occurred in a skinned leg, it was assumed to be localized to the muscles.

Our present knowledge of the intracerebral representation of the sympathetic vasodilator system suggests that the observed peripheral responses may have been of the same character as those in the present investigation; i.e., they included activation of sympathetic vasodilator fibers in the muscles.

LUND (1943, 1945) made similar observations, also in cats, that stimulation in the region of the sulcus cruciatus produced vasoconstriction in the skin and vasodilatation in the extremity muscles. In his opinion, however, the latter reaction was secondary, and due to activation of the baroceptors via the concurrent rise of blood pressure.

It is difficult to comment on the quantitative aspects of the observed reactions. In most cases the vasoconstrictions in the skin and splanchnic region appear to have been of such extent as to more than compensate the decrease of peripheral resistance in the muscles. The adrenal activation was not of such magnitude that the secreted catechols had more than a slight supporting effect parallel with the nervous components. The significance of the anesthetic with regard to the relative proportions of the components has already been discussed.

Summary and Conclusions

With the use of the Horsley-Clarke technique, cats anesthetized with Dial were subjected to electrical stimulation in the mesencephalon with bipolar electrodes. The blood pressure as well as the blood flow in different vascular areas were recorded, and changes produced by stimulation were studied. Stimulation in the tectum mesencephali elicited a substantial increase of the blood flow in the skeletal muscles. When the blood flow was recorded in skin and viscera, it generally showed a coincident decrease. The blood pressure response varied, sometimes rising and sometimes falling; in some experiments no change was observed. As

regards the components of the reaction pattern, the following conclusions are drawn:

1. Unilateral stimulation in the tectum mesencephali may produce bilateral vasodilatation in the muscles. The vasodilatation appears coincidently in the muscles of both the forelegs and hind legs. The concurrent vasoconstriction in the skin is also bilateral.

2. The increase of blood flow in the skeletal muscles is due to activation of sympathetic vasodilator nerves. These sympathetic vasodilator fibers are cholinergic. The effects are blocked by atropine, 0.1-0.2 mg per kg, and are potentiated by eserine, 0.1 mg per kg. Dihydroergotamine, 0.5 mg per kg, does not affect the vasodilatation.

3. The decrease of blood flow in skin and intestines is due to activation of sympathetic vasoconstrictor nerves. These are directly activated by the mesencephalic stimulation and not as a result of reflexes. The effects are not influenced by atropine, but are totally blocked by Dihydroergotamine, 0.5 mg per kg.

4. The adrenal medulla is activated coincidently with activation of vasodilator nerves to the muscles and vasoconstrictor nerves to skin and viscera. The secretion of catechols produces dilatation of muscle vessels and constriction of cutaneous vessels. As regards the vascular responses, this humoral factor is quantitatively of minor importance compared to the nervous components.

CHAPTER III

Localization of the Stimulated Vasomotor Structures in the Mesencephalon and Adjacent Parts of the Brain

In the earliest investigations of autonomic representation in the mesencephalon, no attempts were made to localize active structures more exactly.

The more recent investigations into the anatomy of the mesencephalon with respect to vasomotor functions include, notably, those of the RANSON group. These workers investigated the brain stem systematically point by point with the Horsley-Clarke technique, and in histologic examination of brains they localized the stimulated points, which were marked on charts.

Another method of studying the localization of intracerebral pathways is to produce a particular response by stimulation and to observe whether it persists or disappears after section of various structures. This method, too, was employed in some investigations conducted by the RANSON group, in which they studied, among other things, the mesencephalic localization of vasomotor pathways descending from the hypothalamus.

These two methods of localizing regions with a particular function and their efferent pathways often implement each other, and both were employed in the present investigation.

Methods

Material and Anesthesia

The material in the histologic part of this investigation consisted of 28 brains from cats used in various experimental series. The other part, consisting of acute experiments with an intracerebral section technique, comprised eight cats weighing 2.5-4.8 kg. The anesthesia did not differ from that described in the preceding chapter.

Preparation of the Animal, Stimulation and Recording Technique

The experiments were in principle of the same type as those described in the foregoing, and the preparation was similar. Preparation of the head for stimulation, etc. in experiments with section of various parts of the brain stem was more laborious, however, since inspection of the superficial mesencephalic structures was required. In some experiments a large part of the occipital lobes was exposed and the dura reflected after a Y-shaped incision on either side of the sagittal sinus. The brain substance was removed by careful aspiration through a slender glass tube (1.5 mm in diameter). The falx cerebri was left intact. When the medial parts of the occipital lobes and the posterior portion of the corpus callosum had been removed, the superior colliculi and anterior part of the inferior colliculi were exposed. The dorsal portion of the latter was concealed by the tentorium cerebelli. Minor hemorrhages from the traumatized surfaces of the brain were arrested with pieces of gelfoam. A heating lamp prevented cooling of the exposed parts of the brain.

In other experiments inspection of mesencephalic regions was facilitated by a posterior approach. After drilling of the occipital bone including the crista lambdoidea, the bulk of the cerebellum was aspirated. In no case could traumatization of the transverse sinus be avoided, but the bleeding was arrested by means of bone wax. The whole of the rhomboid fossa, the posterior meatus of

the aqueductus Sylvii, and the caudal surface of the inferior colliculi could thereafter be visualized. By means of a fine burr the tentorium cerebelli was carefully released from its lateral attachment and removed, after which the occipital lobes could be raised with a spatula, thus ensuring a better view. Occasionally there were venous hemorrhages from the dura that were difficult to arrest.

In these experiments the stimulation was generally applied anterior to the mesencephalon, the technique being the same as described earlier. Sections at various levels in the mesencephalon were made, during the course of the experiments, with thin scalpels of varying type. In those cases where mesencephalic portions of the brain were removed during the experiment, this was done with the previously employed aspiration technique. After the experiments the location and extension of the sections in the mesencephalon were checked by macroscopic examination. Furthermore, these brains were also subjected to histologic examination.

Recording of blood pressure and blood flow was done in the manner described earlier.

Histologic Technique

In a number of cases the brain was fixed when the experiment had concluded. This was generally done by perfusion with a 10 per cent formalin solution, injected into the carotids. In order to make the electrode channels more distinct, the electrode was often left in position, i.e., with the tip in the last stimulated point. In some cases electrocoagulation of the stimulated point with direct current had been done too. After fixation the dead animal was left in the Horsley-Clarke apparatus overnight. The electrode was withdrawn the following day and the brain removed for preservation in 10 per cent formalin.

Frozen frontal sections 50 microns thick were taken from the relevant portions of the brain, every effort being made to keep them parallel with the direction of the electrode. Every second

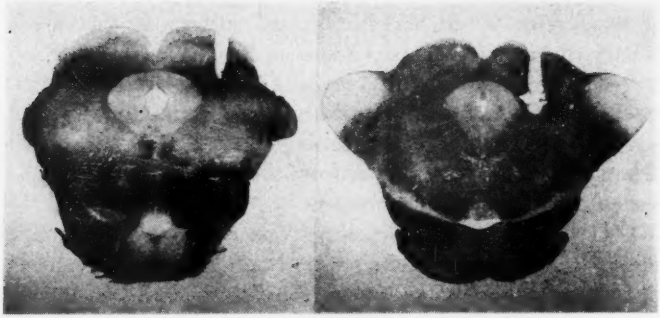


Fig. 33. Histological frontal sections through the mesencephalon and the pons from two different brains, showing electrode channels. After the experiments the electrodes had been left in position and both brains had been fixed in situ with formalin. In the right section the stimulation point had been coagulated (20 mA sec.). (Scale 2.5: 1.)

or every fourth section was retained and stained with hematoxylin *ad modum* Weil (WEIL, 1928). The electrode channels were readily identifiable at microscopic examination, provided there were not too many of them. Similarly, the position of the electrode tip could be localized, most easily and accurately in those cases where the electrode had not been advanced deeper than to the responsive point sought, and of course when the stimulated point had been coagulated. This latter manipulation caused a spherical lesion round the electrode tip. Figure 33 shows two histologic sections with electrode channels. In both cases fixation was done with the electrodes left in position; in the right section electrocoagulation had been carried out.

Results

1. Histologic Examination

Although the Horsley-Clarke technique often permits satisfactory localization of the stimulated points, experience showed that this was not always the case. The electrodes were relatively fine and hence rather flexible. Due, for instance, to tensions

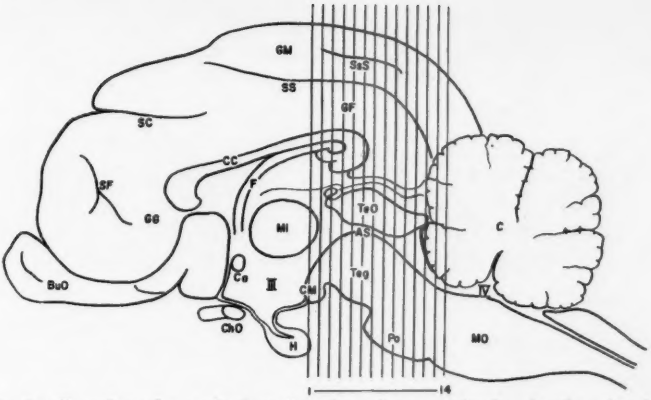
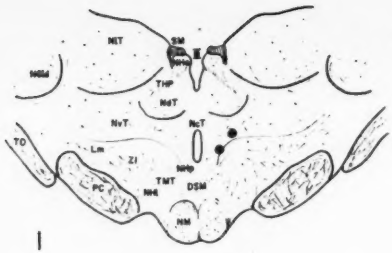


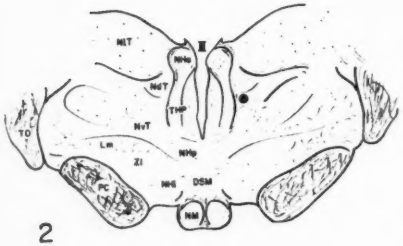
Fig. 34. Drawing of a sagittal section through a cat's brain, showing the site of frontal sections 1-14 in fig. 35. The plane of the sections coincides with the electrode plane in hypothalamic and mesencephalic stimulation. (Scale 1.6: 1.)

in the dura they occasionally descended obliquely into the cerebral tissue. Localizing of the stimulated structures therefore required histologic examination of the brains and identification of the electrode channels.

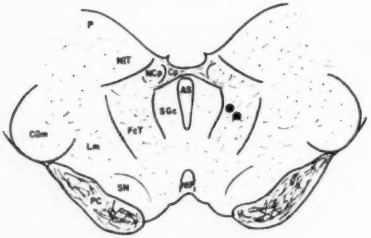
Of the brains that were histologically examined, 28 are included in the results reported below; for only those were taken in which electrode channels and stimulated points could be identified beyond doubt. In most cases identification was simple, for in general the brains contained only a few electrode channels, and some a single channel. All of the identified points had given, when stimulated, a characteristic increase of blood flow in some sector of the skeletal muscles, usually amounting to at least 100 per cent. The vasodilatations elicited from most of the stimulated points had been blocked with atropine, after which the experiments had been concluded and the brains fixed. The part of the brains examined extended from the caudal part of the diencephalon to the rostral portion of the medulla oblongata (figure 34). The points found were plotted on a series of charts in the frontal plane of the brain stem, drawn from a series of histologic sections (figure 35). (For more detailed charts, reference should be made to e.g. WINKLER and POTTER, 1914; MONNIER, 1943; JASPER and AJMONE-MARSAN, 1954.)


MLT
SM
III
NMd
THP
NgT
NvT
NcT
TO
Lm
ZI
NHp
TMT
DSM
PC
NHi
NM

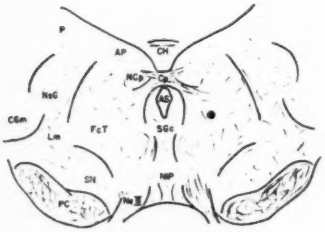
1


MLT
III
NHp
NgT
THP
NvT
TO
Lm
ZI
NHp
PC
NHi
DSM
NM

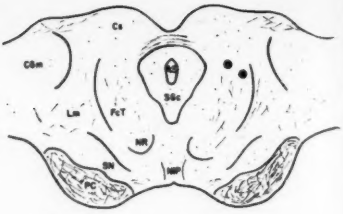
2


P
MLT
NCp
Ce
AS
SGc
FcT
CBm
Lm
SN
PC
PAq

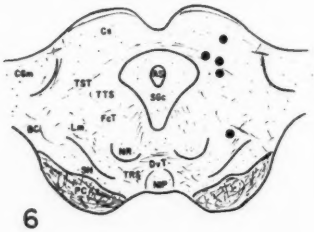
3


P
AP
CH
NCp
Ce
NgC
CBm
Lm
FcT
SGc
SN
NIP
PC
PAq III

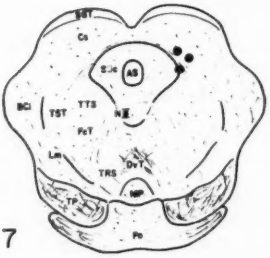
4


Cs
CBm
SGc
Lm
FcT
NR
SN
NIP
PC

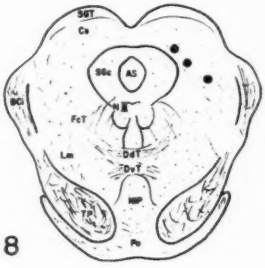
5


Cs
CBm
TST
TTS
SGc
FcT
BCi
Lm
NR
SN
TRS
DvT
NIP
PC

6


SGT
Cs
AS
BCi
TST
TTS
III
FcT
Lm
DvT
TRS
NIP
Tr
Po

7


SGT
Cs
SGc
AS
BCi
III
FcT
Lm
DdT
DvT
NIP
Tr
Po

8

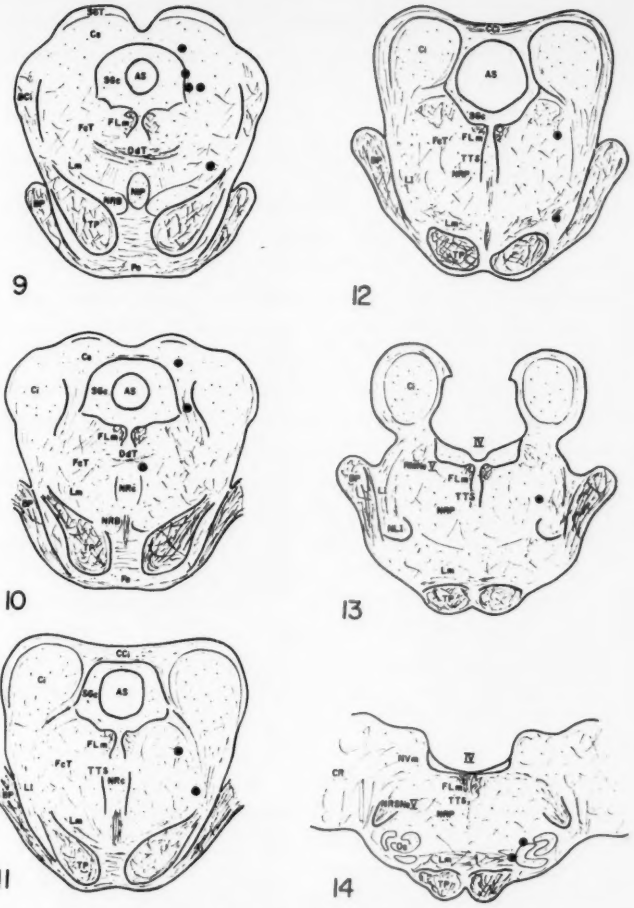


Fig. 35. Series of drawings of frontal sections through the mesencephalon and adjacent parts of a cat's brain. The distance between two sections is 1 mm. Histologically localized stimulation points are represented by the black circles. The level in the brain of each section, 1-14, is shown in fig. 34. Section 1 approximates to frontal plane 8 in the Horsley-Clarke coordinates (JASPER and AJMONE-MARSAN, 1954). (Scale 2.5: 1.)

AP	Area pretectalis
AS	Aqueductus Sylvii
BC	Brachium conjunctivum cerebelli
BCi	Brachium colliculi inf.
BP	Brachium pontis
BuO	Bulbus olfactorius
C	Cerebellum
Ca	Commissura anterior
CC	Corpus callosum
CCi	Commissura collicul. inf.
CGl	Corpus geniculatum lat.
CGm	Corpus geniculatum med.
ChO	Chiasma opticum
CH	Commissura habenularum
Ci	Colliculus inferior
CM	Corpus mamillare
Cp	Commissura posterior
CR	Corpus restiforme
Cs	Colliculus superior
CS	Corpus striatum
DdT	Decussatio dorsalis tegmenti Meynert
DSM	Decussatio supra-mamillaris
DvT	Decussatio ventralis tegmenti Forel
F	Fornix
FcT	Fasciculus centralis tegmenti
FC	Fasciculus cuneatus
Fi	Fovea inferior
FLm	Fasciculus longitudinalis med.
FR	Fossa rhomboidea
Fs	Fovea superior
GF	Gyrus fornicatus
GG	Gyrus genualis
GM	Gyrus marginalis
H	Hypophysis
Ll	Lemniscus lateralis
Lm	Lemniscus medialis
MI	Massa intermedia
MO	Medulla oblongata
NeIII	Nervus oculomotorius
NIII	Nucleus nervi oculomotorii
NcT	Nucleus centralis thalami
NCp	Nucleus commissurae post.
NdT	Nucleus dorsalis thalami
NGld	Nucleus geniculatus lat. dors.
NHa	Nucleus habenularis
NHl	Nucleus hypothalamicus lat.
NHp	Nucleus hypothalamicus post.
NIP	Nucleus interpeduncularis
NlT	Nucleus lateralis thalami
NLl	Nucleus lemnisci lat.
NM	Nucleus mamillaris
NR	Nucleus ruber
NRB	Nucleus reticularis Bechterew
NRc	Nucleus reticularis centr.
NRP	Nucleus reticularis pontis
NRSNeV	Nucleus radicis spinalis nervi trigemini
NsG	Nucleus suprageniculatis
NvT	Nucleus ventralis thalami
NVm	Nucleus vestibularis med.
O	Obex
Os	Oliva superior
P	Pulvinar
PC	Pedunculus cerebri
Po	Pons
RMNeV	Radix mesencephalica nervi trigemini
SC	Sulcus cruciatus
SF	Sulcus falcialis
SGc	Substantia grisea centr.
SGT	Stratum griseum tecti
SM	Stria medullaris
SN	Substantia nigra
SsS	Sulcus suprasplenialis
SS	Sulcus splenialis
T	Thalamus
Teg	Tegmentum
TeO	Tectum opticum
THP	Tractus habenulo-peduncularis
TMT	Tractus mamillo-thalamicus
TO	Tractus opticus
TP	Tractus pyramidalis
TRS	Tractus rubro-spinalis
TST	Tractus spino-tectalis
TTS	Tractus tecto-spinalis
ZI	Zona inserta
III	Ventriculus tertius
IV	Ventriculus quartus

In the posterior part of the diencephalon the responsive area was located immediately dorsal to the posterior hypothalamic nucleus (figure 35: 1). Caudal thereto the vasodilator points were situated somewhat more dorsally, in the ventro-medial part of the thalamus, just lateral to the tractus habenulo-peduncularis (figure 35: 2). At the level of the posterior commissure the vasodilator pathway continued dorso-caudad, ending in the superior colliculus. Of the vasodilator points identified, the majority were found in the basal parts of the superior colliculus and adjacent regions. They seemed to be scattered over a somewhat more diffuse area. The reason why so many points were found here may be that in most experiments the electrode was directed towards that region; for experience had shown—even before the histologic investigation—that the chances of striking structures whose stimulation would produce vasodilatation were greater in that region than in more rostral or more caudal areas. The vasodilator points there were generally localized 3-4 mm below the dorsal surface (figure 35: 6-9). Most of them were found 3-5 mm from the midline just outside the dorso-lateral border of the substantia grisea centralis. The extension of the responsive area was greatest in the dorso-ventral direction, this being especially the case in the caudal portions. At the level of the inferior colliculus the vasodilator pathway appeared to descend rather steeply ventrad. Several points were located in the vicinity of the lemniscus lateralis. None of the identified points were located, however, in the gray matter of the inferior colliculus; the nearest ones were just medial thereto, between that structure and the substantia grisea centralis. The most ventral points were in the pons, dorso-lateral to the tractus pyramidalis, and in the rostral part of the medulla oblongata dorso-lateral to the tractus pyramidalis and ventro-medial to the oliva superior.

If we regard the points that are inserted on the frontal sections in figure 35 as lying along an efferent pathway running through the mesencephalon, and we try to join them from one section to another, we find that the pathway thus formed is fairly well localized. If these histologic findings be considered together with the experience from a large number of other experiments in which localization of vasodilator points showed similar results—partly

with the use of the Horsley-Clarke coordinates and partly by macroscopic inspection—approximately the following picture will emerge of the course and extension of the responsive pathway. The pathway extends through the posterior portions of the hypothalamus up towards the superior colliculus. The difficulties which, in stimulation in that region, were encountered in finding vasodilator responsive structures, in spite of systematic exploration, suggest that the pathway here is confined to a fairly narrow zone. In the basal parts of the superior colliculus a somewhat wider area is taken up, extending through the greater part of the tectum, though narrowing somewhat caudad. The further course of the pathway was more difficult to trace, though at pontine level there were vasodilator points located ventrally, dorsolateral to the tractus pyramidalis. Responsive structures were also found further rostrally in the tegmentum, but with almost the same position in relation to the tractus pyramidalis. Between this ventral extension and the tectal distribution there were a few points suggestive of connections between those areas. Roughly speaking, the efferent pathway from the tectal area may thus be conceived of as a diffuse outflow running directly ventrad from the whole extension of that area, and collecting again in the tegmentum and pons as a narrow bundle of fibers running caudad, adjacent to the tractus pyramidalis and retaining that position in its course towards the medulla oblongata.

Comment

As mentioned above, the current view as to the localization of vasomotor active and silent zones in the mesencephalon is largely based on experiments with stimulation similar to that in the present investigation but with only blood-pressure variations as criteria of the vasomotor responses. Due to the shortcomings of this recording technique—showing, as it does, only the resultant of various components in the peripheral responses—no definite conclusions can be drawn with regard to these. It is, therefore, difficult to compare the present findings with those of earlier investigations. However, the reaction pattern often included a minor change of blood pressure one way or the other, so that some comparison may still be justified.

A study of cerebral charts in the papers of RANSON *et al.* (KABAT, MAGOUN and RANSON, 1935; WANG and RANSON, 1939 a), indicates that the most marked pressor structures were localized dorsal and lateral to the nucleus ruber in the fasciculus centralis tegmenti, though also around the aqueductus Sylvii in the substantia grisea centralis. Numerous pressor points, however, were diffusely scattered over the greater part of the transverse section of the mesencephalon, including the basal portions of the superior colliculus. Depressor reactions had also been elicited from these regions as well as lateral to the fasciculus centralis tegmenti.

Findings closely consistent with these results have been reported by other workers (HESS, 1938, 1947, 1948; MCQUEEN, BROWNE and WALKER, 1954; THOMPSON and BACH, 1950).

A comparison of the localization of the vasodilator points reported in this chapter and the vasomotor active area described in the papers of RANSON and others, shows that the latter area is located more ventrally, although some overlapping exists. It is probable, therefore, that only a few of the stimulation points marked by those authors were associated with activation of sympathetic vasodilator pathways to the muscles (and coincidently of vasoconstrictor pathways to other vascular areas). These must accordingly be regarded as only a minor part of the vasomotor neurons located in the mesencephalon.

2. Section Experiments

Even though histologic investigation of the stimulated points had given a picture of the localization of the structures from which sympathetic cholinergic vasodilator nerves to skeletal muscles and sympathetic vasoconstrictor nerves to skin and intestines could be activated, several questions as to the anatomical organization still remained to be answered. These notably included problems relating to the hypothetical decussation of vasodilator fibers. Stimulation in the tectal structures generally gave rise to bilateral responses. The vasodilatations produced in skeletal muscles by hypothalamic stimulation were also bilateral (ELIASSON,

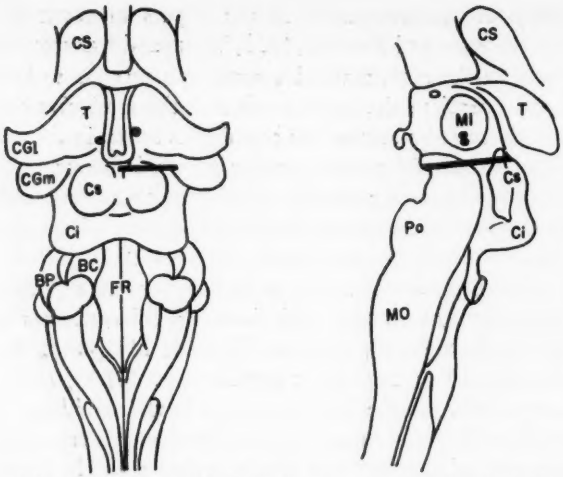


Fig. 36. Schematic drawings of the brain stem, dorsal and sagittal views. The stimulation points are represented by the black circles. The frontal section, immediately anterior to the mesencephalon on the right side, is marked. (For explanation of the experiment see text. The peripheral responses are shown in fig. 37.) (Scale 1.4: 1.)

Folkow, Lindgren and Uvnäs, 1951; Eliasson, Lindgren and Uvnäs, 1954). On the other hand, stimulation of the medullary portion of the vasodilator pathway induced only ipsilateral effects (Lindgren and Uvnäs, 1953 b). The same applied to stimulation in the pons; for in some of the experiments where the stimulated points, according to the histologic examination, were located in the pons dorso-lateral to the tractus pyramidalis, the blood flow was recorded from the muscles of both hind legs and vasodilatation was found only in the ipsilateral extremity. These findings imply, therefore, that some kind of cross connection must exist somewhere between the tectal region and the pontine and medullary portion.

With a view to exploring this problem and others associated therewith, some experiments were undertaken in which either certain parts of the mesencephalon were excised or various sections were made, the responses to stimulation being observed before and after these measures.

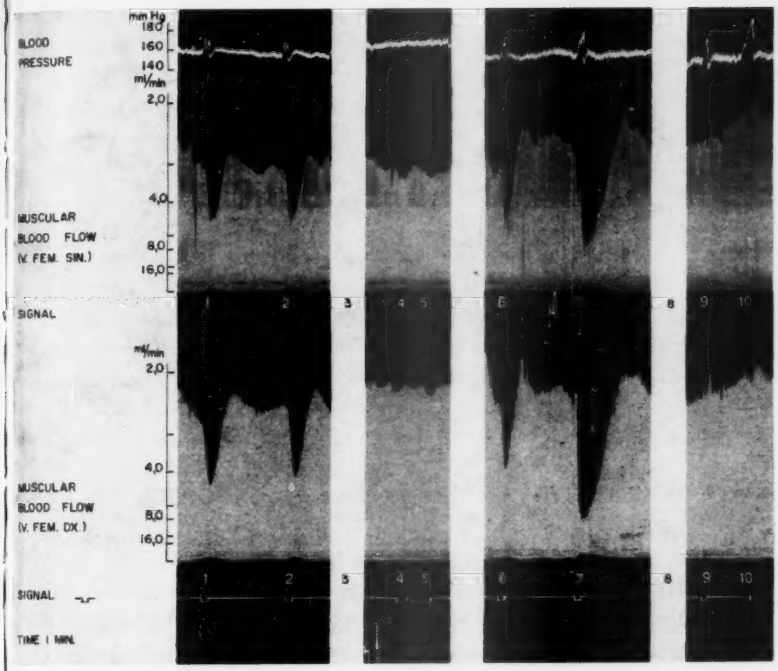


Fig. 37. Cat 4.8 kg. Dial 60 mg/kg. Aa. carotides commun. occluded. Vasodilator responses in the muscles of the hind legs to stimulation in the posterior hypothalamus. Effect on the responses of frontal section of the right brain stem immediately anterior to the mesencephalon (see fig. 36).

1. Stimulation, right, 3.0 V, 20 sec.
2. „ — „ „ „ „ „ „
3. Section.
4. Stimulation, right, 3.0 V, 30 sec.
5. „ — „ „ „ „ 1-2 mm ventral and dorsal to the former point, moving electrode.
6. Stimulation, left, 2.5 V, 20 sec.
7. „ — „ „ 3.5 „ „ „
8. Atropine 0.2 mg/kg I.V.
9. Stimulation, left, 2.5 V, 15 sec.
10. „ — „ „ 3.5 „ 20 „

Note the disappearance of the vasodilator responses in both legs to stimulation on the right side after section.

In one such experiment the vasodilator pathway was stimulated on the right side, 2 mm from the midline, in the posterior part of the hypothalamus. The stimulated points and extension of section are shown in figure 36 and the peripheral responses in figure 37. The stimulation induced bilateral vasodilatation. With

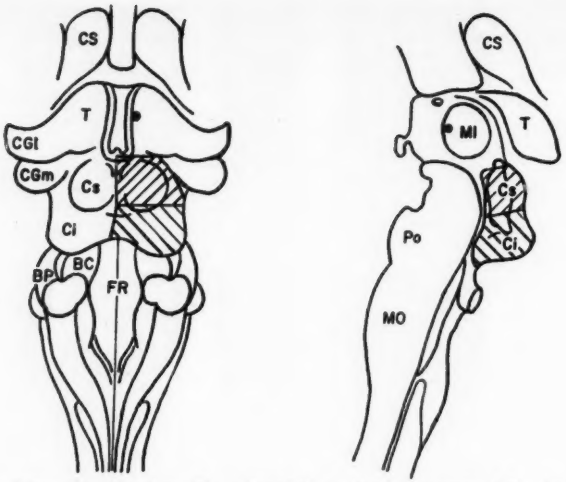


Fig. 38. Schematic drawings. The stimulation point is represented by the black circle. The areas removed, first the colliculus inf. dx. and later in the experiment the colliculus sup. dx., are shaded. (For explanation of the experiment see text.) (Scale 1.4: 1.)

the aim of interrupting the vasodilator pathway on this side, a scalpriform instrument was advanced through the cerebral tissue to the base of the skull. Its position and that of stimulated points were determined by postmortal inspection and histologic examination. The section extended transversely from the midline 6 mm to the right, passing through the anterior border of the superior colliculus to the posterior part of the corpus mamillare. Further stimulation at the same point as before no longer produced vascular effects. This obviously implies that the hypothetical decussation would be located caudal to the section and that no connections exist in the posterior hypothalamus between the pathways on either side. When the electrode was moved to a point 2 mm to the left of the midline, stimulation once more produced vasodilatation in both extremities (6 and 7 in figure 37). The left hypothalamofugal vasodilator pathway was accordingly intact. Atropine blocked the effect as usual.

In another experiment activity was similarly induced in the sympathetic cholinergic vasodilator nerves to both hind legs by

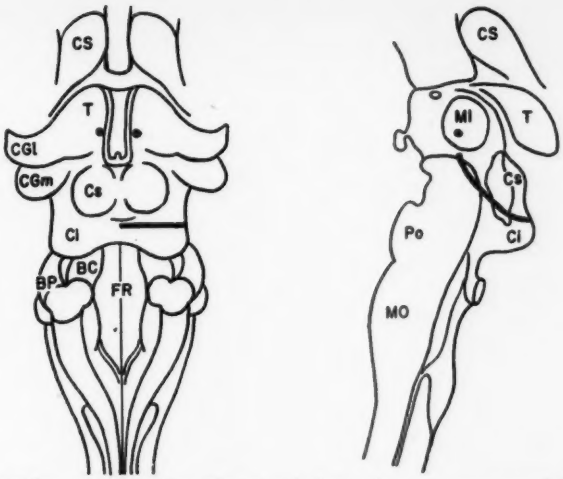


Fig. 39. Schematic drawings. The stimulation points are represented by the black circles. The section through the base of the colliculus sup. dx. is marked. (For explanation of the experiment see text.) (Scale 1.4: 1.)

stimulation of the right vasodilator pathway between the anterior hypothalamus and the mesencephalon (figure 38). By means of suction through a fine glass tube, the right inferior colliculus and caudal portion of the right superior colliculus were first removed. Further stimulation after this operation still elicited bilateral vasodilatation, though quantitatively it was somewhat less. One explanation of this may be that a part of the efferent outflow was damaged. The whole of the right superior colliculus was then excised. Stimulation at the same point as before now produced no responses in either of the legs. In order to preclude the possibility that the electrode tip had been displaced, stimulation was also given ventral and dorsal to the original position; but no vasodilatation could be elicited from there either. This experiment lends weight to the view that the vasodilator pathway from the hypothalamus runs via the tectum mesencephali. Having regard to the fact that only that area was removed, it is probable that the pathway runs via the tectum mesencephali alone.

Figure 39 shows stimulated points and section in a further experiment—also with stimulation of the vasodilator pathway

on the right side in the posterior hypothalamus. The responses were bilateral. The direction of section through the dorsal part of the mesencephalon will be seen from the figure. Extending from the anterosuperior portion of the right inferior colliculus ventrorostrad under the basal parts of the right superior colliculus, the section must have severed the connections running ventro-caudad from the latter. On the other hand, the connections were not disturbed from the right superior colliculus and adjacent structures in the medial direction above the aqueductus Sylvii. Stimulation at the same point as before and in its environment elicited, after this operation, substantially reduced vasodilator effects on both the ipsilateral and the contralateral side. Shifting of the electrode to a corresponding point on the left side in the hypothalamus had the same effects—even quantitatively—as the original ones, i.e., bilateral vasodilatation. The latter could be blocked with atropine in the usual way. Stimulation was associated with minor rises of blood pressure—10-20 mm Hg.

The observations made in this experiment may seem somewhat bewildering. Why did bilateral vasodilatation—albeit so reduced that the increase of flow was not more than one-half to one-third of the original one—occur after section in response to stimulation on the right side? Was it due to connections from the right to the left side in the hypothalamus, to fibers passing ventral to the section, to connections above the aqueductus Sylvii between the right and left part of the tectum, or was it passive to the rise of blood pressure? The first two possible explanations seem unlikely in view of the conclusion drawn from the experiments illustrated in figures 37 and 38. The fourth possibility may explain a part, though not the whole, of the increase of blood flow; for stimulation on the left side produced, after atropine, a similar rise of blood pressure but a smaller increase of flow. The explanation, therefore, may probably lie in commissural connections in the tectum. The principal conclusion from this experiment is, however, that the major part of the decussation is located ventral to the aqueductus Sylvii.

The experiment could not, however, be taken as direct proof of the localization of this decussation to the tegmentum or pons. For this reason a few experiments were conducted with in-

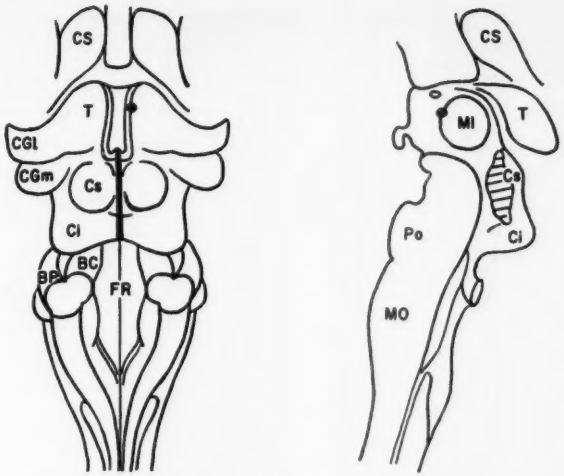


Fig. 40. Schematic drawings. The stimulation point is represented by the black circle. The sagittal section through the tectum mesencephali (dorsal to the aqueductus Sylvii) is marked. (For explanation of the experiment see text.) (Scale 1.4: 1.)

creasingly deep sagittal incisions into the mesencephalon until the decussation was reached. One of them is shown in figure 40. The connections between the two sides of the tectum mesencephali were interrupted dorsal to the aqueductus Sylvii. This caused no change of the reaction pattern in stimulation of the right vasodilator pathway between the anterior hypothalamus and the tectum; for bilateral vasodilatation occurred after the section too. The experiment provides further evidence that the decussation is to be sought ventral to the aqueductus Sylvii.

This view was also supported by the results of experiments in which the sagittal section had a greater extension ventrad. These are evident from the observations in the experiment in respect of which the stimulated points and section are illustrated in figure 41, the peripheral responses being shown in figure 42. On stimulation of the diencephalic portion of the vasodilator pathway on the right side just rostral to the mesencephalon, pronounced vasodilatation was elicited in the muscles of both hind legs (1 and 2 in figure 42). The increase of flow, though of somewhat lesser mag-

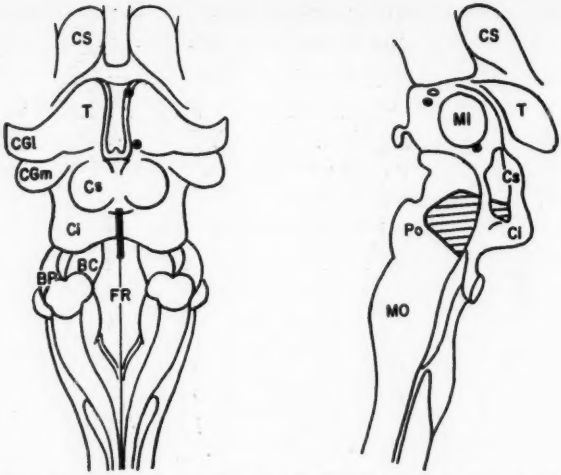


Fig. 41. Schematic drawings. The stimulation points are represented by the black circles. The sagittal section through the commissura coll. inf., posterior part of the tegmentum and dorsal part of the pons is marked. (For explanation of the experiment, see text. The peripheral responses are shown in fig. 42.) (Scale 1.4: 1.)

nitude in the contralateral extremity, was nevertheless quite pronounced. Similar responses were occasionally found in mesencephalic stimulation, too, as pointed out in the foregoing. After the sagittal section that involved the commissura colliculorum inferiorum and caudal portion of the tegmentum down to the pons, with the greater part of the decussatio dorsalis tegmenti as well as the caudal part of the decussatio ventralis tegmenti and some of the nucleus interpeduncularis and nucleus reticularis centralis, the response to stimulation at the same point as before was altered. The vasodilatation was unchanged in the right leg but absent in the left. The implication may be that section had severed the partial decussation. The exact localization of the latter is not easy to say; experiments of the same type as that described here, but with less extensive sections, did not yield unequivocal results. With the technique employed it was difficult, during the acute experiment, to determine exactly, in advance, the length and depth of the section. It seems likely, however, that the crossing

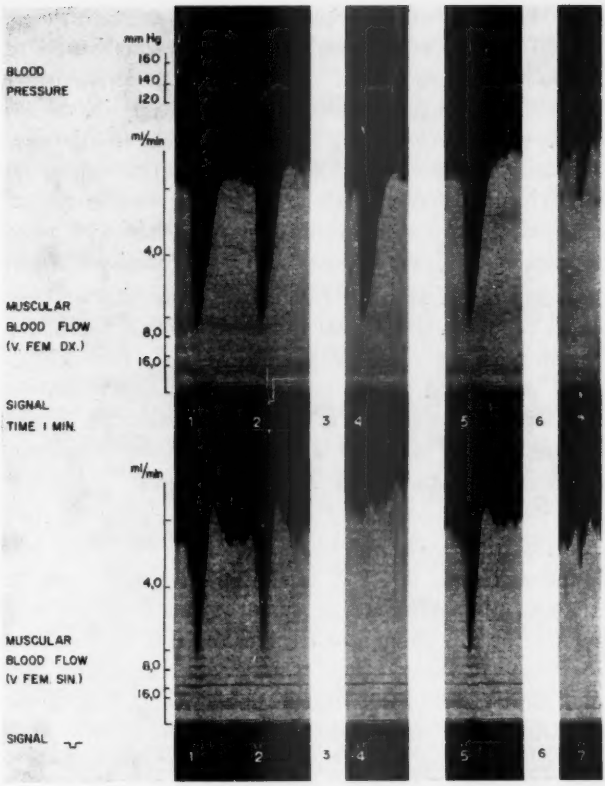


Fig. 42. Cat 3.5 kg. Dial 40 mg/kg. A. carotis commun. sin. occluded. Vasodilator responses in the muscles of the hind legs to stimulation in the posterior and the anterior hypothalamus (at the supraoptic level). Effect on the responses of sagittal section in the mes- and metencephalon (see fig. 41).

1. Stimulation, right post. hypothal., 3.5 V, 15 sec.
2. „ — „ „ „ „ „ „ „ „
3. Section.
4. Stimulation, right post. hypothal., 3.5 V 15 sec.
5. „ — „ „ ant. „ „ „ „ „
6. Atropine 0.2 mg/kg I.V.
7. Stimulation, right ant. hypothal., 3.5 V, 15 sec.

Note the disappearance of the vasodilator responses in the contralateral leg to stimulation in the posterior hypothalamus after section.

exists in the region of the decussatio dorsalis tegmenti, dorsal to the caudal portion of the nucleus interpeduncularis and to the decussatio ventralis tegmenti, and that it extends longitudinally several millimeters caudad, dorsal to, and possibly in, the nucleus reticularis centralis. A finding that lends weight to this view is a histologically identified vasodilator point in that region (figure 35: 10). The fact that vasodilator responses were, in general, so seldom elicited on stimulation in this region might be explained by postulating a diffuse crossing with a low density of fibers.

According to the above (figure 39), a connection between the two sides possibly exists dorsal to the aqueductus Sylvii. As will be evident from the present experiment (figures 41 and 42), such a dorsal decussation would only be of secondary importance. Even though the major part of the dorsal connection was intact, no increase of flow occurred in the contralateral leg on stimulation after interruption of tegmental decussations.

In the continued course of the relevant experiment the electrode was shifted further rostrad and stimulation was given with its tip in the supraoptic region of the anterior hypothalamus. It was still located on the right side, about 1 mm from the midline. Stimulation at this point now elicited bilateral vasodilatation of approximately the same extent as before (5 in figure 42). Bearing in mind the results of an investigation by ELIASSON, LINDGREN and UVNÄS (1954), showing that in the dog the anterior hypothalamus itself contains a relay station for the sympathetic vasodilator pathway with connections between the two sides, this observation is not surprising. It demonstrates that vasodilator impulses elicited by stimulation in the supraoptic region on one side were also effected via contralateral hypothalamic structures. The cat, too, may have in this region an integrative center where e.g. cortical impulses could be relayed.—After atropine the vasodilatation was blocked in both extremities.

Comment

The question as to possible crossing of autonomic pathways in their course in the brain stem and spinal medulla has always been the subject of discussion. As regards the sympathetic hypothalamo-

fugal pathways in the cat, KARPLUS and KREIDL (1911) considered that they reached to the cervical sympathetic bilaterally via a cross connection in the upper thoracic segments. MAGOUN, RANSON and HETHERINGTON (1938) found, also in cats, that a minor part of the vasomotor (pressor) pathway crossed cranial to the first cervical level, while the greater part reached the spinal medulla uncrossed (*vide* also MAGOUN, 1940). They obtained their results by observing rises of blood pressure on hypothalamic stimulation before and after hemisections of the brain stem at various levels between the superior colliculus and the first cervical segment. HARRISON, WANG and BERRY (1939), in hypothalamic stimulation of unilaterally sympathectomized cats before and after hemisection at various levels, showed that pressor impulses from the hypothalamus might run uncrossed to the spinal medulla or cross in the brain stem or in spinal segments below the cervical ones. They even found it probable that impulses could reach the ipsilateral side after having crossed twice.

The observation of LINDGREN and UVNÄS (1953 b) that activation of the sympathetic vasodilator pathway in its medullary course produced only ipsilateral effects, suggests that it does not cross either in its medullary or in its spinal portion. This is clearly different from other hypothalamofugal vasomotor pathways, which are considered to have a component that crosses at spinal level. Its lowest decussation, according to what has been found in the present investigation, is located in the mesencephalon and pons. As is usual with autonomic pathways, it is of partial type.

Whether a connection also exists between the two sides dorsal to the aqueductus Sylvii does not seem to be fully clear, but such a hypothesis is also supported by an observation made by LINDGREN, ROSÉN, STRANDBERG and UVNÄS (1955). On one occasion they succeeded in activating sympathetic vasodilator nerves in a dog upon stimulation at a midline point in the commissura colliculorum superiorum.

Whether the accompanying vasoconstrictor neurons also have the same course with regard to decussation has not been shown, although there is much to suggest that this is the case. According to Chapter II (figure 12) the vasoconstrictor effects elicited in the

skin from the tectum mesencephali were bilateral, but according to Chapter V (figure 53) the cutaneous effects produced by activation of the vasodilator pathway in the medulla oblongata were unilateral. This suggests that the vasoconstrictor neurons described have a course analogous to the vasodilator pathway, even with regard to decussation in the mesencephalon and pons. Evidently, therefore, there are several different types of hypothalamofugal (or mesencephalofugal) vasoconstrictor pathways, insofar as their anatomical course in the central nervous system is concerned. There are completely uncrossed pathways, pathways with diffuse decussation in the brain stem (hypothalamus—mesencephalon—pons—medulla oblongata); the pathway studied here, with a crossing in the mesencephalon—pons; and, lastly, pathways that cross at different spinal levels. It is difficult to say whether these cross connections can be regarded as fiber decussations proper; abundant synapses and short neurons may doubtless be found in the connections between the two sides.

Discussion

Histologic examination enables a good idea to be obtained of the mesencephalic extension of the sympathetic vasodilator structures. The continuity rostrad with corresponding active structures in the posterior hypothalamus (according to this investigation and another one conducted by ELIASSON, FOLKOW, LINDGREN and UVNÄS, 1951), and also caudad with the medullary sympathetic vasodilator region (LINDGREN and UVNÄS, 1953 b), suggests that the mesencephalic vasodilator area constitutes a part of the hypothalamofugal sympathetic vasodilator pathway. This is further supported by the section experiments in the second part of this chapter, which showed that sympathetic dilator impulses elicited from the hypothalamus descend only via the tectum mesencephali.

There has been some diversity of opinion as to the localization of the hypothalamofugal pathways in the brain stem (for more

detailed presentation, *vide* RANSON and MAGOUN 1939; MAGOUN, 1940; WHITE, SMITHWICK and SIMEONE, 1952). Many workers have considered the main path of these fibers to be the fasciculus longitudinalis dorsalis, from dorso-medial, ventro-medial and posterior hypothalamic nuclei, via the substantia grisea centralis in the mesencephalon, to different vegetative nuclear areas in the medulla oblongata and spinal medulla. Another pathway, also medial, was suggested by BEATTIE, BROW and LONG (1930 a, b) who, in degeneration studies, showed that most of the fibers from the posterior hypothalamus passed through the medial part of the reticular formation and in the fasciculus longitudinalis medialis.

These "medial" views have been strongly criticized, however, by RANSON and his co-workers. The results of stimulation and section experiments led those authors to conclude that the hypothalamofugal fibers passed the mesencephalon very diffusely, though with some concentration to the lateral part of the tegmentum. "*In the midbrain descending connections which mediate impulses induced by hypothalamic stimulation occupy a wide area in both the central and the tegmental region*" (MAGOUN, RANSON and HETHERINGTON, 1938). Their results, as pointed out elsewhere, were reached in a study of pressor responses.

Little attention seems to have been given to the fact that some hypothalamofugal fibers—not only the recently discovered sympathetic vasodilator fibers but also vasoconstrictor ones—in the dorsal portion of the hypothalamus and ventral part of the mesencephalon run dorso-lateral towards the tectum. BEATTIE, BROW and LONG (1930 a) nevertheless reported that a small number of the hypothalamofugal connections had that extension towards the superior colliculus.

The sympathetic vasodilator pathway described here passes, in its course caudad, through the lateral part of the tegmentum, in which several authors found both pressor- and depressor-active structures (e.g. KABAT, MAGOUN and RANSON, 1935; WANG and RANSON, 1939 a; THOMPSON and BACH, 1950). In the pons and the rostral part of the medulla oblongata the pathway has a distinct position in the ventro-lateral portion. This contrasts with the diffuse organization of hypothalamofugal pressor fibers in

those parts of the brain: "*In the medulla the hypothalamic efferent pressor pathway occupies a large area in the lateral reticular formation*" (WANG and RANSON, 1939 b).

Aside from the observation that the adrenal medulla may be activated coincidently with sympathetic vasodilator fibers on stimulation in tectal regions, no attempt was made here to elucidate the related problems of localization. As regards the pathways descending to the adrenals from the hypothalamus, HARRISON, WANG and BERRY (1939) reached the following conclusion: "*The data suggest that such an efferent pathway differs in no essential way from that of vasomotor and cervical sympathetics.*" This implied, in their opinion, that the pathways might run uncrossed, or might cross in the brain stem or in spinal segments below the cervical level.

The adrenal medullary responses described in Chapter II: 9 coincided with activating of the vasodilator and vasoconstrictor fibers that have been discussed. It seems plausible, therefore, to assume that the localization in the tectum mesencephali as well as the descending pathway are consistent with those applying to these fibers.

Summary and Conclusions

The experimental animals' brains were examined histologically, and stimulated points from which cholinergic sympathetic vasodilator nerves may have been activated were localized and plotted on frontal charts. In order to study further the mesencephalic extension of active regions, sections of various parts of the brain stem were made in acute experiments. The effect of stimulation proximal to the section site was observed before and after the operation. The following conclusions were drawn with regard to the intracerebral localization of the sympathetic vasodilator pathway (probably they also apply to neurons the activation of which produces vasoconstriction in skin and viscera as well as secretion of catechols from the adrenals):

1. The responsive area is located in the basal parts of the superior colliculus, whence the pathway continues ventro-caudad to the upper part of the medulla oblongata, where it descends dorsolateral to the tractus pyramidalis.

2. The mesencephalic region is a part of the hypothalamofugal vasodilator pathway. It is continuous rostrally with the sympathetic vasodilator area in the hypothalamus and caudally with the corresponding area in the medulla oblongata.

3. The tectofugal pathway has a partial crossing, located ventral to the substantia grisea centralis approximately in the region of the decussatio dorsalis tegmenti. A minor connection may also exist between the two sides dorsal to the aqueductus Sylvii.

CHAPTER IV

Character of the Vasomotor Areas in the Mesencephalon and their Efferent Pathways in the Medulla Oblongata

It has been possible in the dog, as pointed out earlier, to trace the intracerebral course of the sympathetic vasodilator pathway from the motor cortex. ELIASSON, LINDGREN and UVNÄS (1954), in hypothalamic stimulation of chronically decorticated dogs, were able to activate sympathetic vasodilator nerves, which observations were designed to demonstrate that neurons referable to that system had their origin in the anterior hypothalamus. This finding was consistent with some earlier experiments conducted by KARPLUS and KREIDL (1910) and MAGOUN (1938), who also demonstrated that vasomotor reactions—changes in blood pressure—could be elicited from the hypothalamus in decorticated dogs.

Histologic studies with a degeneration technique have led to the conclusion that hypothalamofugal pathways consist of neurons varying in length. BEATTIE, BROW and LONG (1930 a, b) thus showed that after lesions of the posterior hypothalamus—which regions gave vasomotor responses (blood pressure reactions) when stimulated—degenerated fibers could be detected which ended in the mesencephalon, medulla oblongata and spinal medulla. Having regard to possible synapses, nothing is known of the course of the sympathetic vasodilator pathway caudal to the hypothalamus.

Histologic examination of brains enables the stimulated points to be rather accurately localized. In general, however, this examination does not permit of any valid conclusions regarding the

character of the stimulated neurons. The question has to be asked: Were the present responses the results of activation of afferent or efferent tracts to and from centers located elsewhere, or did the stimulation occur in a region of nuclear character with cell bodies and synapses? This question is particularly justified in the case of the mesencephalon, with its complicated structure. Although even a rather superficial study of relatively thick histologic sections, and still more so a careful study of the cytoarchitecture, may throw some light on the problem, it will seldom warrant assured conclusions. For a more functional investigation of the problem, various approaches are available. One of them is to produce a small lesion in a region from which a desired response has been elicitable, and then leave the animal for a time so that interrupted fibers will degenerate peripheral to the lesion. These fibers can later be studied with a special histologic technique. Another approach is to use a neurophysiologic method, for instance with a study of conduction times. A third possibility lies in interruption of the connections with higher centers and, after a sufficient interval for cut fibers to degenerate, exploration of the regions distal to the section with a stimulation technique. If animals treated in this way show the same responses as intact ones, the activated structures cannot only be efferent fibers from higher centers.

The following experiments for the purpose of studying the post-hypothalamic course of the sympathetic vasodilator pathway (and also that of the accompanying vasoconstrictor neurons and adrenal-activating neurons) were based on this latter principle.

Methods

Material

Successful experiments were performed on 11 chronically decerebrated cats (weight 2.2-3.6 kg), 6 decerebrations being of bilateral supracollicular type and 5 of unilateral infracollicular type.

Anesthesia

It was found advantageous, in the acute experiments, to give the supracollicularly decerebrated cats light anesthesia, as a result of which the motor activity was mitigated on account of weakened reflexes. The animals received 20-25 mg Dial per kg intravenously.

Those cats which had undergone unilateral infracollicular decerebration were treated, with regard to anesthesia, as ordinary intact animals (see Chapter II).

Preparation of the Animal and Stimulation, Recording and Histologic Technique

The experimental procedure did not diverge from those types described in Chapter II; nor did the preparation of the cats. As regards the cranial measures the supracollicularly decerebrated cats were generally prepared for stimulation in both the mesencephalon and the medulla oblongata; for mesencephalic stimulation was sometimes found difficult due to scar tissue, pieces of gelfoam and silver clips in the operative field—all of which handicapped insertion of the electrodes.

In the experiments on the infracollicularly decerebrated cats, stimulation was done only in the medulla oblongata. The existing defect in the occipital bone was enlarged caudad as far as the membrana atlanto-occipitalis, and remaining parts of the cerebellum were removed.

The stimulation and recording techniques were quite unchanged.

When the experiment had been concluded, the brains were fixed with formalin. The position and extent of the decerebration section were checked macroscopically and the silver plate removed. Similarly, relevant parts of the brain were inspected histologically for identification of stimulated points and for more accurate determination of the decerebration trauma.

Supracollicular Decerebration. At the start of the series of operations the cats were anesthetized with Nembutal (30 mg per kg intraperitoneally). However, this drug produced, after decerebration and the attendant elimination of all higher centers, such deep and prolonged anesthesia that postoperative complications caused a very high mortality.

A controllable anesthetic, ether, was therefore adopted, although this method was more laborious. The cats were initially anesthetized with ether on an open mask, and after muscular relaxation a tracheal tube was inserted through which an air and ether mixture could then be administered. This administration was terminated immediately after the decerebration section. In order to reduce the salivation during operation and for a time thereafter, 0.1 mg atropine per kg was given intramuscularly about half an hour before operation.

A longitudinal incision was made through the depilated skin over the dome of the skull, after which the parietal bones were freed of galea and temporal muscles. The periosteum was removed with a raspatory, and a hole a few square centimeters in size was then made in the parietal bones with a dentist's drill. The dura was opened with T-shaped incisions on either side of the sagittal sinus, and stay sutures were applied in its flaps. The falx cerebri was then divided, major hemorrhages being prevented by application of silver clips. To facilitate orientation of more basal cerebral structures, those parts of the hemispheres were removed which covered the dorsal part of the corpus callosum and mesencephalon; layer after layer of the brain substance was coagulated by diathermy, then aspirated.

The most formidable problem associated with actual section of the brain stem lay in the major hemorrhages that were difficult to arrest. A good way of coping with this was to insert rapidly a piece of a metal plate having no sharp edges. A suitable appliance of this kind had been prepared in advance out of 0.5 mm gauge sheet silver, 15-20 mm in width and with the lower edge fashioned to the contours of the base of the brain. This silver plate was then left undisturbed in the brain. After careful hemostasis a loose

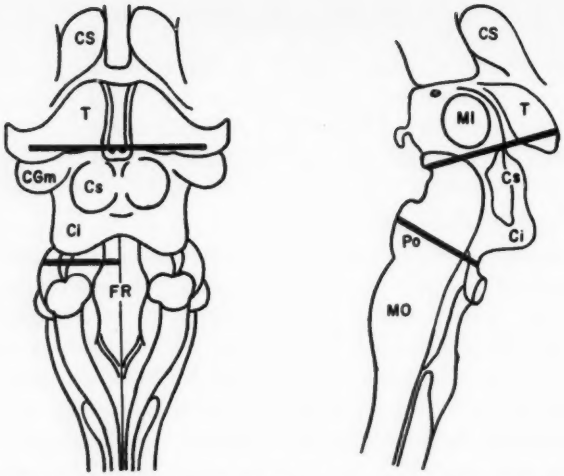


Fig. 43. Schematic drawings of the brain stem, dorsal and sagittal views, showing the sites of the two types of decerebration sections, bilateral supracollicular and unilateral (left) infracollicular section. (Scale 1.4: 1.)

tamponade of gelfoam was placed over the wound surfaces of the hemispheres, the dura then being sutured. The two temporal muscles were sutured together in order to form some protection over the defect in the cranium. The skin wound was closed with continuous steel sutures. The position of the decerebration section just anterior to the mesencephalon is shown in figure 43.

In most cases the operation resulted in almost total section of the brain stem, but to avoid waste of time and labor on the postoperative tending of incorrectly operated animals the position of the silver plate was checked roentgenographically a day or so after the operation.

The postoperative management of the cats was very exacting. In the early postoperative period there was a major risk of aspiration, and the animals were therefore kept under almost constant observation. Since, moreover, their heat regulation had been lost they were placed in heated cabinets regulated by thermostats. In general a cabinet temperature of 26-28° C was adequate for maintaining the rectal temperature at 37-39 degrees. The latter

temperature was checked and annotated every two or three hours, day and night, until the experiments began.

As a check on the fluid balance the cats were weighed once or twice a day. During the first three days they received fluid only parenterally in the form of 75-200 ml saline per kg subcutaneously. Thereafter they were tube fed three times daily with a mixture of 40-80 ml milk and finely chopped fish. Fluid too was administered parenterally when required. The bladder function was checked and vesical puncture done if required. Bronchial toilet was also carried out whenever necessary. To combat the danger of infection, 100,000 I.U. penicillin was administered daily.

Those cats that were subsequently used in acute experiments had been tended in this way between 6 and 16 days.

Infracollicular Decerebration. The cats received ether anesthesia, and the operative technique accorded in principle with that in supracollicular decerebration. The operation was performed caudal to the tentorium cerebelli. The crista lambdoidea and parts of the occipital bone were removed, together with the ventral portion of the cerebellum. The silver plate was inserted just behind the inferior colliculus and approximately in the middle of the pons, so that the entire left half of the brain stem was cut (see figure 43). Roentgenograms were taken.

Since half the brain stem in these cats was quite intact, the postoperative management did not need to be quite so meticulous as in the others; but to be on the safe side most of the same precautions were taken. The duration of postoperative management varied from 4 to 9 days.

In both types of decerebration the mortality was high. Acute experiments could be carried through in only 11 of the 24 cats that survived the operation itself. A common cause of death was intracerebral bleeding in the operative field; another was affection of the respiratory system. Pulmonary affection of pneumonic type was often found at autopsy. A contributory cause of this may have been aspiration of saliva and regurgitated gastric contents.

Denervation of Fore Paw. In one of the cats that had undergone supracollicular decerebration, the right foreleg was denervated by the method described in Chapter II, this operation being done without anesthesia 6 days after decerebration.

Results

1. Mesencephalon

In five experiments on cats that had undergone supracollicular decerebration, successful attempts were made to elicit vasomotor responses by mesencephalic stimulation. The interval between the operation and the acute experiment varied between 6 and 16 days.

In two of these experiments both the muscle blood flow and the cutaneous blood flow were recorded in order to study whether any change occurred in the reaction pattern.

Figure 44 shows the result of an experiment in which the cat had been decerebrated 14 days previously. The muscle blood flow was recorded from both hind legs. Bilateral vasodilatation (1, 2 and 3 in the figure) occurred on stimulation in basal parts of the right superior colliculus about 4 mm caudal to the decerebration section. After atropine the effects were quite absent. The responses in this experiment, as will be seen, were of the same character as those elicited by similar stimulation in a cat with intact cerebrum. The vasodilator responses had the same latency and duration, and the effect of atropine suggested their cholinergic nature. Possibly it could be objected that the increase of flow was perhaps of somewhat smaller magnitude than that with corresponding stimuli in experiments on non-decerebrated cats. Conceivable reasons for this are discussed below.

It might also be asked whether the other features of the reaction pattern appeared in decerebrated animals. The experiment illustrated in figure 45 answers this question in the affirmative, insofar as the cutaneous vasoconstriction is concerned. Although the decrease of flow on stimulation was not very pronounced, it was nevertheless quite distinct. That it could not have been a case of a compensatory decrease, due for example to mechanical factors, is evident from the facts that it occurred despite the rise of blood pressure and was unchanged after the muscle vasodilatation had been blocked with atropine. Hence it must have been a case of active vasoconstriction. It may even be worthy of note that in this experiment the stimulation was given in the left part of the tectum mesencephali. Yet the recorded responses were

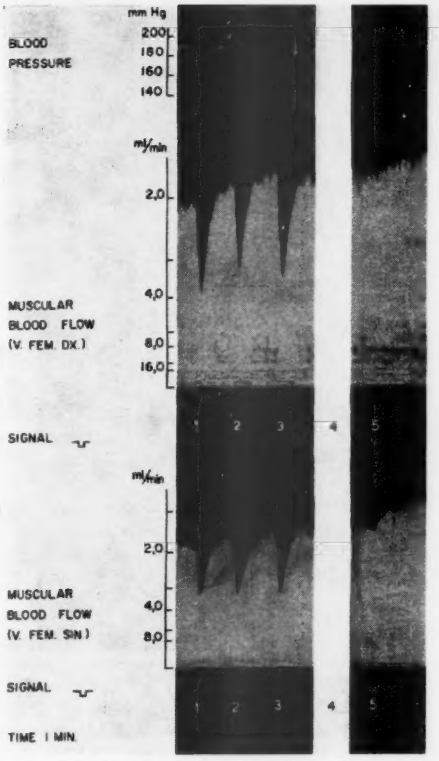


Fig. 44. Cat 2.0 kg. Dial 25 mg/kg.
Supracollicular decerebration 14 days before the experiment.
Aa. carotides commun. occluded. Nn. vagi cut.
Vasodilator responses in the muscles of both hind legs to stimulation in the right part of the tectum mesencephali.

1. Stimulation, 2.5 V, 15 sec.
2. „ — „ „ „ „ „
3. „ — „ „ „ „ „
4. Atropine 0.2 mg/kg I.V.
5. Stimulation, 2.5 V, 15 sec.

referable to the right half of the body, the effects thus being contralateral.

Due to the relatively few experiments in this series, no intestinal blood flow was recorded. The question whether mesencephalic stimulation in supracollicularly decerebrated animals produced vasoconstriction in that area cannot, therefore, be answered.

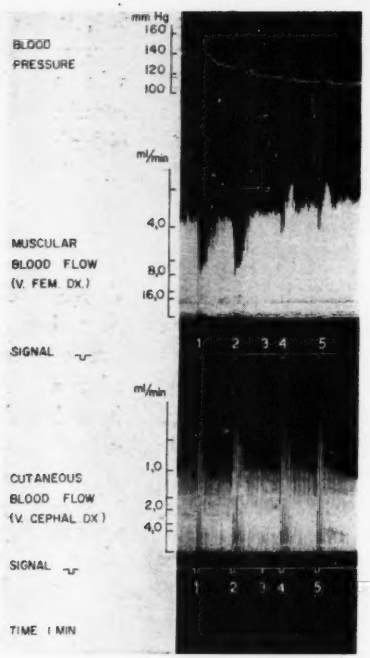


Fig. 45. Cat 2.5 kg. Dial 30 mg/kg.
Supracollicular decerebration 6 days before the experiment.
Aa. carotides commun. occluded. Nn. vagi cut.

Vasodilator responses in the muscles of the right hind leg and vasoconstrictor responses in the skin of the right foreleg to stimulation in the left part of the tectum mesencephali.

1. Stimulation, 3.0 V, 10 sec.
2. „ — „ „ „ „ „
3. Atropine 0.2 mg/kg I.V.
4. Stimulation, 3.0 V, 10 sec.
5. „ — „ „ „ „ „

However, the adrenal component was studied in one experiment. In Chapter II: 9 a method was described of studying the effect of adrenal activation via the increased sensitivity of vasomotor denervated vascular areas to adrenal medullary hormones. In the experiment illustrated in figure 46 the cat had undergone supracollicular decerebration 16 days earlier. Six days thereafter the nerves to the right foreleg had been cut in the axillary fossa. The muscle blood flow from the right hind leg and the cutaneous

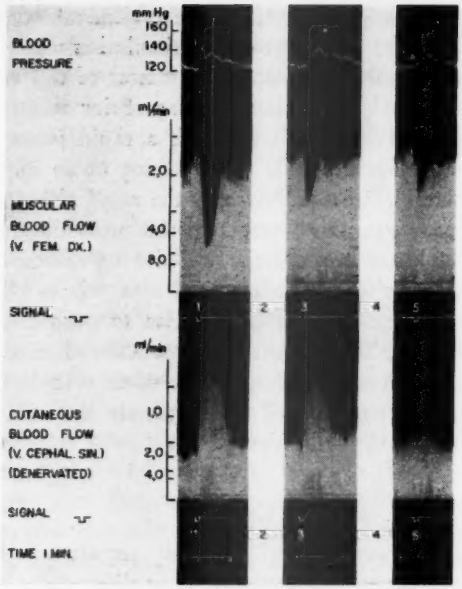


Fig. 46. Cat 2.1 kg. Dial 30 mg/kg.
Supracollicular decerebration 16 days before the experiment.
Right foreleg denervated 10 days before the experiment.
Vasodilator responses in the muscles of the right hind leg and vasoconstrictor responses in the skin of the right foreleg to stimulation in the right part of the tectum mesencephali.

1. Stimulation, 3.5 V, 10 sec.
2. Atropine 0.1 mg/kg I.V.
3. Stimulation, 3.5 V, 10 sec.
4. Adrenals removed.
5. Stimulation, 3.5 V, 10 sec.

Note that the vasoconstriction in the denervated foreleg disappeared after removal of the adrenals.

flow from the denervated right fore paw were recorded. On stimulation with 3.5 volts in the right part of the tectum mesencephali a few millimeters caudal to the decerebration section, pronounced vasodilatation occurred in the muscles. In the denervated leg considerable vasoconstriction appeared, and was of comparatively long duration. After atropine, 0.1 mg per kg, the muscle vasodilatation was substantially reduced but the vasoconstriction was virtually unchanged. This vasoconstriction disap-

peared almost entirely, however, after bilateral adrenalectomy. The blood pressure response to each stimulation was a minor rise. A detailed study showed that the character of this response was somewhat changed after adrenalectomy. Prior thereto the blood pressure rise had been biphasic, with a rapid phase during the stimulation itself and a slow phase lasting up to a minute or so after stimulation. Subsequently only the rapid phase was present. The explanation of this phenomenon is probably that the first phase of the blood pressure rise was due to vasoconstriction (in the skin and, probably, the intestinal area) via activity in vasoconstrictor nerves, but the later phase to vasoconstriction via humoral factors. The experiment thus showed that even those neurons in the mesencephalon which, when stimulated, result in secretion of adrenal medullary hormones are still present in chronically decerebrated animals.

Comment

The tectum mesencephali is, with respect to its different afferent and efferent connections, a complicated structure. It was not possible, as pointed out in the foregoing, to identify the vasoactive regions, with well-defined anatomic structures, that were studied here. Hence it is difficult to discuss in detail various tectal nuclear systems and pathways. Moreover, in most investigations dealing with the anatomic organization, functional aspects of the results have not been sufficiently treated to make a comparison worth while. (For details of the anatomy of various systems of pathways, *vide* e.g. RASMUSSEN, 1936; HUBER, CROSBY, WOODBURNE, GILLILAN, BROWN and TAMTHAI, 1943; WOODBURNE, CROSBY and MCCOTTER, 1946; CROSBY and HENDERSON, 1948; CROSBY and WOODBURNE, 1951; MARBURG and WARNER, 1947; BUCHER and BÜRGI, 1950.)

BEATTIE, BROW and LONG (1930 a, b), in a histologic investigation on cats, studied the course of hypothalamofugal pathways. They produced, under aseptic precautions, lesions in the posterior hypothalamus and studied degenerated fibers with the Marchi or the Alzheimer-Mann technique. The observed fibers varied considerably in length. The majority could be traced as far as spinal

segments, even the upper lumbar segments, but some ended at medullary level. The authors, it is interesting to note, also observed short fibers extending no further than to the mesencephalon. "*Some of the fibers are seen to pass laterally and to enter the ventral aspect of the superior colliculus, where they apparently end*" (BEATTIE, BROW and LONG, 1930 a). It cannot, of course, be concluded that these fibers are referable to the sympathetic vasodilator pathway. Probably, however, the regions in which lesions were produced had been vasomotor active, since the authors reported that electrical stimulation there gave rise to changes of blood pressure. Having regard to the extension of the sympathetic vasodilator pathway in the posterior hypothalamus, it is also conceivable that some lesions involved that region too.

The reported results indicate only that neurons with the various functions described have their origin in the tectum mesencephali. It is probable that the fibers descending from the hypothalamus end in synapses with those mesencephalic neurons. As regards the quantitative conditions it is difficult to decide whether all or only a part of the hypothalamic neurons synapse. Conceivable is that some of them continue as far as spinal level; for long hypothalamic neurons of this type are known from degeneration studies (BEATTIE, BROW and LONG, 1930 a, b). However, these hypothalamofugal fibers had a medullary localization different from that of the ventro-lateral vasodilator pathway. In the results described in the foregoing it was pointed out that the peripheral responses in general were quantitatively smaller in decerebrated than in normal cats. This could possibly have been due to a decreased density of neurons in the stimulated region as a result of degeneration of the hypothalamic neurons. Yet it has to be borne in mind, too, that the decerebrated cats were often in poor general condition at the time of the acute experiments.

2. Pons and Medulla Oblongata

It has already been pointed out that according to LINDGREN and UVNÄS (1953 b), unilateral stimulation of the sympathetic vasodilator pathway in its medullary portion only produced

vasodilatation in the ipsilateral muscles. The same authors supposed that this part of the pathway was only of transiting nature, since the pathway in the medulla oblongata is a strictly localized narrow tract just dorso-lateral to the tractus pyramidalis and, having regard to this position in the ventro-lateral portion, an anatomical relationship with e.g. dorsal medullary vasomotor structures in the rhomboid fossa is unlikely.

Since the sympathetic vasodilator pathway studied by LINDGREN and UVNÄS (1953 b) in the medulla oblongata in all probability constitutes, too, the descending connection of the mesencephalic sympathetic vasodilator area as described above, it was considered important, for elucidation of its nature, to throw further light on the character of this medullary pathway.

In two of the aforementioned experiments on cats that had undergone chronic supracollicular decerebration, the medulla oblongata too was explored by stimulation. It was established, among other things, that stimulation in the ventro-lateral part of the medulla oblongata elicited vasodilatation of known character in the skeletal muscles, the distribution being ipsilateral. The result of one of these experiments is shown in figure 47. Histologic examination revealed that the stimulated points were located precisely in those regions—dorso-lateral to the tractus pyramidalis and ventral to the oliva superior, and further caudad just dorso-lateral to the oliva inferior—to which LINDGREN and UVNÄS (1953 b) and LINDGREN, ROSÉN, STRANDBERG and UVNÄS (1955) had localized the extension of the sympathetic vasodilator pathway in that part of the brain. There is considerable evidence, therefore, that this pathway is also the efferent one for those neurons which have been found to have their origin in the tectum mesencephali.

In five cats that had undergone left intracollicular decerebration, similar systematic exploration was undertaken of the portion of the medulla oblongata located caudal to the section level, between the latter and the level of the obex. (The position of the decerebration section is shown in the schematic drawing in figure 43.) The muscle blood flow was recorded in both hind legs. A consistent finding in these experiments was the almost complete absence of vasomotor responses on stimulation in the zone on the

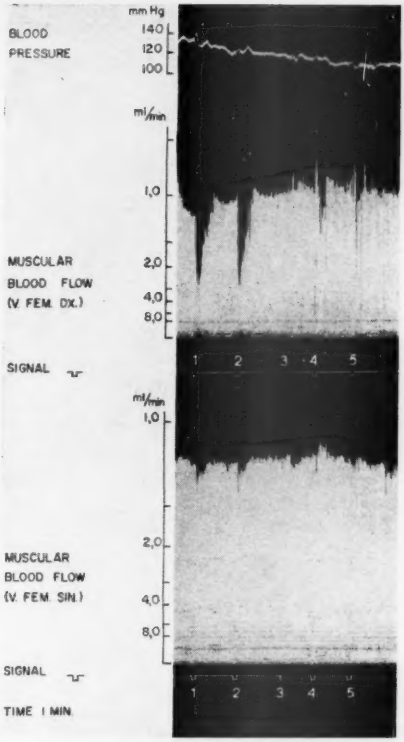


Fig. 47. Cat 3.0 kg. Dial 30 mg/kg.
Supracollicular decerebration 16 days before the experiment.
Sinus caroticus denervated bilaterally. Nn. vagi cut. Artificial respiration.
Vasodilator responses in the muscles of the ipsilateral hind leg to stimulation in the right ventrolateral part of the medulla oblongata.

1. Stimulation, 2.0 V, 10 sec.
2. „ — „ „ „ „ „
3. Atropine 0.2 mg/kg I.V.
4. Stimulation, 2.0 V, 10 sec.
5. „ — „ „ „ „ „

Note the ipsilateral distribution of the responses. No vasodilatation in the muscles of the contralateral leg.

left side behind the section in the anterior part of the medulla oblongata. This zone extended caudally to approximately the middle of the rhomboid fossa. Caudal thereto was a region with somewhat diffusely scattered pressor points. The silent zone

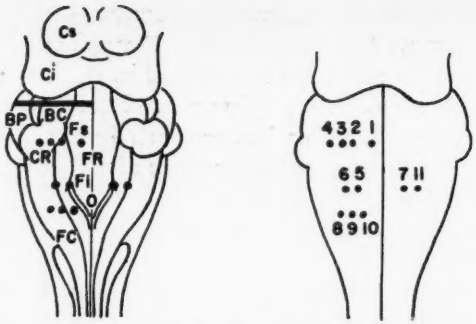


Fig. 48. Schematic drawings of the dorsal aspect of the lower brain stem. The projections of the stimulation points and the decerebration section are marked. The numbers to the right refer to fig. 49. The peripheral responses in the experiment are shown in that figure. (Scale 1.4: 1.)

contrasted with those vasomotor reactions, chiefly of pressor type, that were elicitable in major parts of the medulla oblongata by stimulation on the right side, and by stimulation in intact animals. It should be made clear, however, that although the vasomotor (pressor) structures in the medulla oblongata appeared to be rather scattered, the maximal responses were generally obtained on stimulation in the vicinity of the fovea inferior (*cf.* RANSON and BILLINGSLEY, 1916). This latter finding also applied to stimulation in the left fovea inferior.

In none of the five experiments was it possible, by stimulation in the left half of the medulla oblongata, to induce vasodilatation in skeletal muscles via activation of sympathetic cholinergic vasodilator nerves, even though the ventro-lateral parts were explored very carefully. On the other hand, in three of the experiments control stimulation on the right side did elicit typical vasodilatation, which was confined to the ipsilateral leg (in the fourth experiment no stimulation of this side was performed, in the fifth one no typical vasodilatation could be elicited in spite of systematic exploration).

An experiment of this type is illustrated in figure 49. Seven days before the experiment, this cat had undergone left decerebration just caudal to the inferior colliculus. The muscle blood flow was recorded in both hind legs. The positions of the different

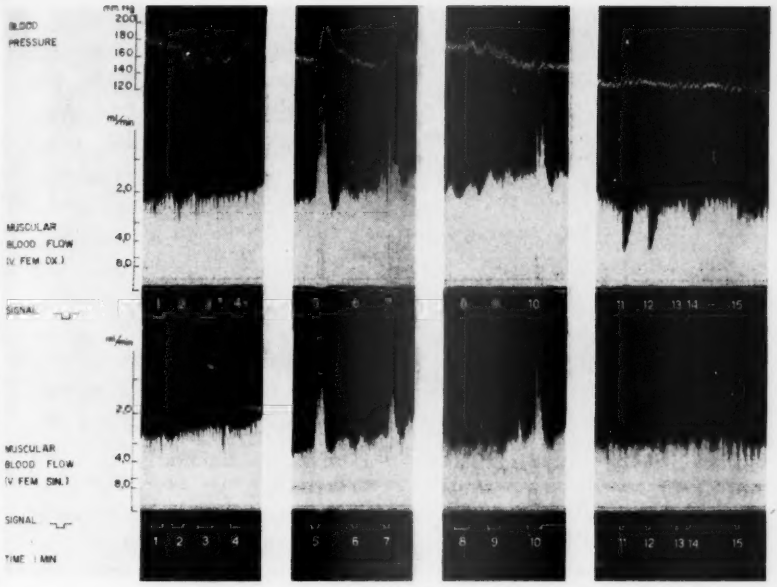


Fig. 49. Cat 2.8 kg. Dial 70 mg/kg.

Left infracollicular decerebration 7 days before the experiment.

Aa. carotides commun. occluded. Nn. vagi cut. Artificial respiration.

Vascular responses in the muscles of the right and left hind legs to stimulation at various points in the medulla oblongata (see fig. 48).

1. Stim., left 1 mm, 4 mm caudal to the section, 2.5 V, 40 sec.
2. „ „ 3 „ „ „ „ „ „ „ „ „ 40 „
3. „ „ 4 „ „ „ „ „ „ „ „ „ 50 „
4. „ „ 5 „ „ „ „ „ „ „ „ „ 40 „
5. „ „ 2.5 „ 9 „ „ „ „ „ „ „ 20 „
6. „ „ 3.5 „ „ „ „ „ „ „ „ „ 15 „
7. „ right 2.5 „ „ „ „ „ „ „ „ „ 15 „
8. „ left 4 „ 11 „ „ „ „ „ „ „ 45 „
9. „ „ 3 „ „ „ „ „ „ „ „ „ 40 „
10. „ „ 2 „ „ „ „ „ „ „ „ „ 45 „
11. „ right 3.5 „ 9 „ „ „ „ „ „ „ 10 „
12. „ „ „ „ „ „ „ „ „ „ „ „ 10 „
13. Atropine 0.2 mg/kg I.V.
14. Stim., right 3.5 mm, 9 mm caudal to the section, 2.5 V, 10 sec.
15. „ „ „ „ „ „ „ „ „ „ „ „ 10 „

Note the impossibility of eliciting vasodilator responses upon stimulation in the left half of the medulla oblongata.

stimulated points—or, more correctly, the electrode channels—will be seen from figure 48, where 1, 2, 3 and 4 represent stimulation on the left side of the medulla oblongata, 4 mm caudal to the decerebration incision. At each stimulation the electrode tip was slowly advanced dorso-ventrad through the cerebral substance to the base of the skull, with continuous stimulation. Each signal thus denotes the time of stimulation along such a channel. At this level no vasomotor responses could be elicited whatsoever; no changes occurred, either in blood pressure or blood flow. When the electrode was shifted further caudad, 9 mm from the section, and advanced into the left inferior fovea, a marked pressor reaction with rise of blood pressure and bilateral vasoconstriction (no. 5) occurred when the tip was 1-2 mm below the dorsal surface. One millimeter lateral to this channel there was once more a silent zone (no. 6). On the right side, too, a similar pressor reaction was elicited by stimulation of a corresponding region (no. 7). Continued exploration 2 mm caudad (nos. 8, 9 and 10) gave no appreciable result; only slight vasoconstriction at one point. On the other hand, the sympathetic vasodilator fibers on the right side were readily found (nos. 11 and 12).

Comment

Numerous tectofugal pathways extending caudad have been described. They vary in length, some being short and ending in various nuclear structures in the tegmentum, others longer and extending to bulbar or spinal level. Some pathways run crossed, some uncrossed, and yet others both crossed and uncrossed. (For a detailed review of the anatomical conditions, see the papers cited in section 1.) The mesencephalo-bulbar course of the sympathetic vasodilator pathway described here does not fully coincide with any of the known tectofugal pathways. Its partial cross connection in the decussatio dorsalis tegmenti accords with the decussation of e.g. the tractus tecto-spinalis. However, the continued course by no means coincides with that pathway, which has a medial location immediately ventral to the fasciculus longitudinalis medialis. Degeneration studies have shown that the tectofugal pathways running ventro-caudad vary somewhat with

regard to the length of the neurons. Thus both crossed and uncrossed tecto-tegmental and tecto-pontine neurons exist. Some of them have in part the same course as the tectofugal vasomotor pathway studied here, e.g. the tractus tecto-reticularis. With the given experimental conditions, however, it cannot be ruled out that tegmental synapses exist in addition to tectal ones.

The failure to elicit any effects by stimulation in the medulla oblongata on the same side as the infracollicular decerebration section suggests that the sympathetic vasodilator pathway had degenerated. Its mesencephalo-bulbar portion would accordingly consist of relatively long neurons and be devoid of bulbar synapses. BEATTIE, BROW and LONG (1930 a, b), as mentioned above, reported that lesions in the posterior hypothalamus caused degeneration of fibers as far down as the spinal medulla. The location of these hypothalamofugal fibers was, in the upper portion of the medulla oblongata, dorso-medial; in the lower portion, caudal to the decussatio pyramidarum, ventro-medial—i.e. an extension quite differing from the ventro-lateral sympathetic vasodilator pathway. This finding also indicates that the latter runs from the tectum mesencephali (or just distal thereto), and thus does not degenerate after lesions of the hypothalamus—as was shown, too, by the experiments on cats which had undergone supracollicular decerebration.

Discussion

The method employed here is based on the well-known fact that the distal portion of severed nerve fibers undergoes trophic degeneration (and the proximal end, to some extent, retrograde degeneration). Histologic methods enable degenerative changes in the damaged fibers to be demonstrated after only one day, and indeed after but a few hours. After a short time these fibers also loose their ability to conduct impulses produced, for example, by electrical stimulation. (With regard to various problems of degeneration, *vide* e.g. CAJAL, 1928.)

In an investigation conducted by FRIEDBERG (1931) into corticofugal vasomotor pathways in the cat, the same principle was

applied. He removed the motor cortex and gave electrical stimulation in the internal capsula. He reported that 6-7 days after decortication the corticofugal vasomotor fibers had totally degenerated and stimulation produced no rises of blood pressure, whereas stimulation five days after the operation had elicited responses. In the present decerebration experiments acute stimulation generally took place 7-10 days after the operation. It should be noted that in some experiments with infracollicular decerebration, functional degeneration had presumably occurred only 4-5 days after the operation.

Probably all components of the reaction pattern—vasodilatation in the skeletal muscles, vasoconstriction in the skin (and the intestines?), and activation of the adrenal medulla—persisted and were elicitable by tectal stimulation in cats that had undergone supracollicular decerebration. This uniformity in the neuronal organization lends weight to the view that the various sympathetic neurons in question constitute a functional entity. The relay station in the tectum mesencephali makes it possible for mesencephalic reflexes to activate them. A number of afferent pathways run to the tectum mesencephali, and hence there should be ample prerequisites for reflexes to be relayed by that route. It suffices to mention tectopetal pathways from the cortex, hypothalamus, thalamus, from the optic pathway, from various bulbar nuclei, from the spinal medulla.

Whether any impulses that pass this region via different pathways are actually relayed also to the tectofugal sympathetic fibers described here is not known, however. As regards one of the components, the adrenal medullary activity, it has been claimed that a reflex center for the adrenals is located at the transition between mesencephalon and medulla oblongata; for CANNON and RAPPORT (1921) observed that decerebration just behind the inferior colliculus blocked reflex activation of the adrenal medulla on stimulation of e.g. the brachial nerve. Both the superior and the inferior colliculi, on the other hand, could be removed without effect. "*These observations place the center immediately back of the corpora quadrigemina in the floor of the fourth ventricle.*" It need not be assumed, however, that CANNON and RAPPORT's reflex activation of the adrenal medulla occurred via

those neurons that run together with the sympathetic vasodilator pathway; adrenal medulla-activating neurons probably exist, too, in the vasomotor (pressor) active structures that are diffusely scattered in the tegmentum and upper part of the medulla oblongata. The location of their "center" also argues against such an assumption.

The functional significance of the sympathetic vasodilator system is discussed further in Chapter VI.

Summary and Conclusions

The vasomotor responses to stimulation in the mesencephalon and medulla oblongata were studied in acute experiments on cats which had undergone chronic supracollicular or infracollicular decerebration. It the case of supracollicular decerebration, mesencephalic stimulation elicited on the whole the same responses as those in intact animals. In the case of infracollicular decerebration, stimulation in the medulla oblongata did not produce any activation of the sympathetic vasodilator pathway. The following conclusions are drawn with regard to the neuronal organization.

1. Neurons referable to the sympathetic vasodilator system have their origin in the tectum mesencephali, as do neurons activating vasoconstrictor nerves to the skin and those activating the splanchnic nerves to the adrenal medulla. Prerequisites therefore exist for the region in the tectum mesencephali to have the function of an integrative center, where e.g. hypothalamofugal impulses are relayed. The active structures are, therefore, not only descending fibers from the hypothalamic neurons.

2. The lowest intracerebral relay station in the sympathetic vasodilator pathway is located in the mesencephalon; for the medullary portion of this pathway has the character of descending tectofugal fibers which degenerate on infracollicular decerebration.

CHAPTER V

Some Aspects of the Functional Significance of the Mesencephalic Vasomotor Area and its Relation to Medullary Vasomotor Centers

Different pathways converge to reticular structures in the medulla oblongata containing the vasomotor center: excitatory and inhibitory pathways, afferent fibers in the spinal medulla, nerves from baroceptors and chemoceptors, and, probably, fibers of various types from higher regions. Although the influence of the various components on the efferent vasomotor outflow can often be studied separately, it is generally difficult or almost impossible to decide their complicated interrelations. One fundamental problem lies in the significance of the mesencephalofugal vasomotor neurons, studied in the present investigation, in relation to this bulbar system. Observations made there and by LINDGREN and UVNÄS (1955) suggest that the vasodilator pathway passes the medulla oblongata uninterrupted and without connection to the vasomotor center. Whether the same applies to the accompanying vasoconstrictor neurons remains to be elucidated. Regardless of whether these are relayed as excitatory neurons to the bulbar vasoconstrictor center or run directly to spinal neurons, the question remains, as with the vasodilator neurons: Do they, in the regulation of peripheral resistance, interfere with, for instance, baroceptor reflexes and maintenance of vascular tone?

Methods

Material and Anesthesia

The series consisted of 21 cats (weight 2.1-4.3 kg). They were anesthetized with Dial in the manner described in Chapter II.

Preparation of the Animal and Stimulation, Recording and Histologic Technique

The stimulation and operative measures carried out in this part of the investigation were concerned not only with the mesencephalon but also, in great part, with the medulla oblongata and pons. To facilitate visualization of this region, the overlying parts of the cerebellum were in most cases removed. A heating lamp prevented cooling of the exposed portions of the brain.

The decerebration sections just caudal to the inferior colliculi in some experiments were performed with a small scalpel. Although great care was taken to avoid traumatizing basal arteries, bleeding often occurred; the blood was then collected and reinfused to obviate changes in the circulating blood volume.

In some experiments the dorsal parts of the medulla oblongata were destroyed by thermocautery. Bleeding was moderate. The cauterized tissue was removed by suction. The extent of the lesion in one of the experiments is evident from figures 55 and 56.

Other preparatory measures taken here were as described in Chapter II.

The same stimulation and recording technique as before were employed.

For clarification of the position and extent of the lesions, and for identification of stimulated points, several brains were histologically examined with the previously used technique.

Results

1. Influence of the Mesencephalic Vasomotor Area on "Normal" Vascular Tone

Many different factors are concerned in the regulation of vascular tone. Opinions as to their interrelations have varied. As regards the nervous factors, most researchers today consider that the vasoconstrictor nerves play the principal role. These have, under all conditions, some impulse flow, some tone. In the normal animal vasoconstrictor tone is considered to be governed from the vasoconstrictor center in the medulla oblongata. If the connections between that center and the periphery are interrupted, the result will be an immediate loss of vascular tone and hence vasodilatation. This is the case, for example, in spinal cord lesions and in sympathectomy. However, the normal vascular tone is more or less rapidly restored in that spinal centers give rise to some vasoconstrictor tone or the smooth muscle cells in the vascular walls acquire their own tone. Even very early investigations, with the use of a section technique, served to demonstrate the essential importance of the medulla oblongata to vascular tone. Thus DITTMAR (1870, 1873) and OWSJANNIKOW (1871) demonstrated in animal experiments, as was pointed out in Chapter I, that section of the brain stem anterior to the medulla oblongata did not influence the blood pressure. But when the section was made just caudal to that part of the brain, the blood pressure fell to very low values. The cause of this was the generalized vasodilatation resulting from total loss of vasoconstrictor tone.

As regards a continuous impulse flow in sympathetic vasodilator nerves—vasodilator tone—nothing has been conclusively demonstrated. As mentioned in the foregoing, vasodilator tone was an important feature, it is true, of the dualistic theory propounded by BAYLISS early this century. According to this theory the medulla oblongata also contains a vasodilator center, governing the activity in vasodilator nerves. At that time, however, the existence of sympathetic vasodilator nerves was not taken into

account; rather the discussion was largely concerned with parasympathetic vasodilator nerves and vasodilator fibers in the dorsal roots. BAYLISS's theory has probably been abandoned by most modern workers, now that the existence of an integrative vasodilator center in the medulla oblongata has been found to be unlikely. Although depressor reactions are elicitable from those structures in the posterior part of the rhomboid fossa, near the obex, where the vasodilator center was considered to be located, they do not involve any vasodilator nerves but are due to inhibition of vasoconstrictor tone (FRUMIN, NGAI and WANG, 1953; LINDGREN and UVNÄS, 1954 a). Moreover, the convincing evidence that e.g. the postulated vasodilator fibers in the dorsal roots were not involved in depressor reflexes with a central reflex arc, completely undermined the foundations on which the theory of vascular tone as a result of the balance between vasoconstrictor tone and vasodilator tone was based. Further evidence was recently presented (LINDGREN and UVNÄS, 1955) to show that not even sympathetic vasodilator nerves could be activated from the vasodilator center, and that the medullary portion of the sympathetic vasodilator pathway had no connection with that region.

Several questions nevertheless remain:

First: Do the sympathetic vasodilator nerves normally have any tone; i.e., are the cortical area, the hypothalamic region, and the mesencephalic area in which neurons referable to this system have been shown to exist, tonic centers? If such a basal tone exists in these fibers, is it of a magnitude sufficient to influence the blood flow in the skeletal muscles?

Secondly: Do those vasoconstrictor fibers which can generally be activated from the same region as the sympathetic vasodilator fibers, possess any basal tone? If so, has it any significance relative to normal vascular tone in skin and intestines, and will the loss of it be reflected in the blood flow in those regions?

The questions whether mesencephalic sympathetic vasodilator and vasoconstrictor fibers possess any tone is difficult to answer on the basis of experiments with the technique employed in the present investigation. There is a possibility, on the other hand, of finding out whether the loss of any such tone would influence the blood flow in a vascular area.—A series of experiments was there-

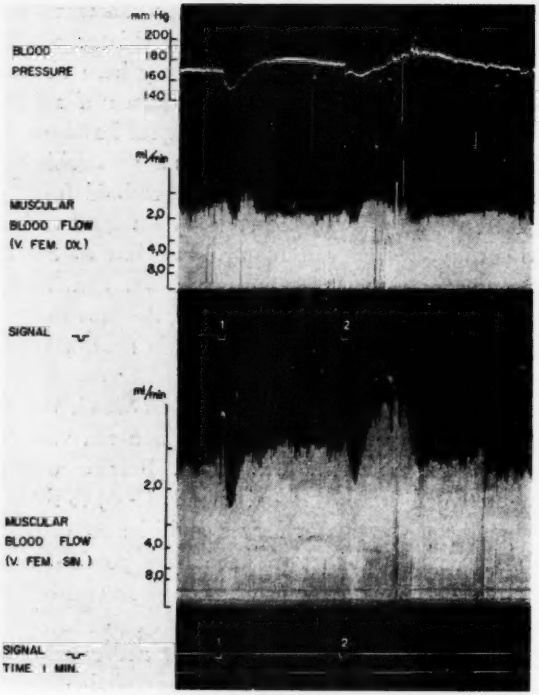


Fig. 50. Cat 2.5 kg. Dial 40 mg/kg.
Aa. carotides commun. occluded. Nn. vagi cut.
Vascular responses in the muscles of the right and left hind legs to acute infracollicular decerebration.
1. Section of the right half of the brain stem below the colliculus inf.dx.
2. Section of the left half at the same level.
Note that the blood flow (i.e., the vascular tone) is unchanged after the operations.

fore conducted in which the brain stem was cut caudal to the mesencephalon during the experiment. The vascular effects could then be observed by recording the blood pressure and the blood flow in different vascular areas.

In some experiments the muscle blood flow was recorded from both hind legs in the usual way. The result of one of them is shown in figure 50. In order to obviate any influence of the

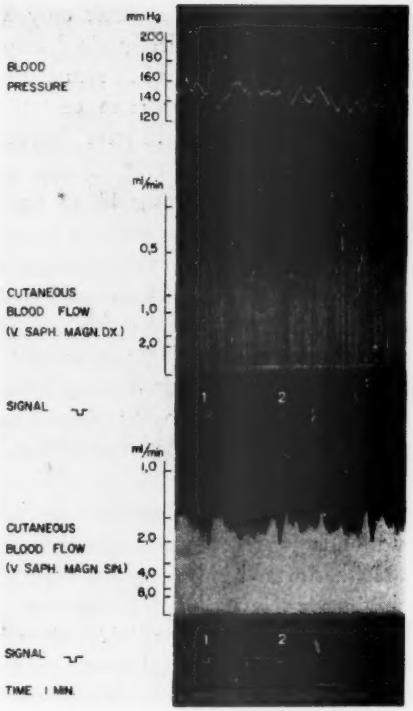


Fig. 51. Cat 2.9 kg. Dial 40 mg/kg.
Acute supracollicular decerebration.
Aa. carotides commun. occluded. Nn. vagi cut.

Vascular responses in the skin of the right and left hind legs to acute infracollicular decerebration.

1. Section of the left half of the brain stem below the colliculus inf.sin.
2. Section of the right half at the same level.

Note that the blood flow (i.e., the vascular tone) is unchanged after the operations.

baroceptor mechanisms, these latter were eliminated before the experiment. Section of the brain stem was done in two stages, one side at a time. The operation itself was attended by minor disturbances in the blood pressure and blood flow. They could have been due to several factors, such as mechanical stimulation of vasomotor fibers with the knife, or adrenal discharge, but did not

affect the evaluation of the results. After only a few minutes the vascular responses were completely similar to those before the sections. If tone had been induced in sympathetic vasodilator nerves from the mesencephalon or from centers located more rostrally, then the blood flow should have decreased when that tone was lost.

In other experiments the cutaneous blood flow was instead recorded in both hind paws. To eliminate the possibility of influence from higher centers, especially the hypothalamus, a few of these experiments were performed on cats which had undergone acute supracollicular decerebration; for STRÖM (1950 a) had reported that the blood flow in the fore paws of the cat sometimes showed a transient increase after decerebration. He demonstrated that this increase was localized to the pads. The phenomenon was interpreted as loss of tone in hypothalamofugal vasoconstrictor fibers serving the heat regulation.

The experiment illustrated in figure 51 was performed on a cat which had undergone supracollicular decerebration a few hours earlier. Neither after hemisection nor after section on both sides of the brain stem just caudal to the mesencephalon was there any change in the blood flow. This might be interpreted to mean that the mesencephalofugal vasoconstrictor fibers are devoid of significance relative to the normal tone of cutaneous vessels.

STRÖM's observation that if the pads themselves were eliminated by ligation, decerebration did not affect the blood flow in the paw, was also confirmed in a few experiments. In contrast to STRÖM's experiments, where intracollicular decerebration was done, infracollicular decerebration, with one side at a time, was carried out here. The results indicate that neither the mesencephalon nor the hypothalamus or higher regions have any significance relative to normal vasoconstrictor tone to the skin of the paw (apart from the pads).

Comment

The method employed for studying tone in vasodilator and vasoconstrictor fibers is far from ideal. It permits of no direct

conclusions, but merely enables one to observe that the mesencephalic regions probably have no continuous influence on the level of the peripheral circulation. But since this latter is in great part a function of vasomotor tone, it has nevertheless been possible to gain some idea of it and to draw the conclusion that there is probably no mesencephalic basal vasomotor tone.

The baroceptors were functionally eliminated at the outset of the experiment. Otherwise these mechanisms would have readjusted the vascular tone if this had changed after section of the brain stem. Thus the term "normal vascular tone" means a steady level of vascular tone, high or low, but under resting conditions in other respects.

It should also be borne in mind that the conception, basal tone in nerve fibers, referred here to a condition in anesthetized animals, and probably is not tantamount to basal tone under physiologic conditions in conscious, intact animals.

The results are in conformity with those early findings which indicated that regions rostral to the medulla oblongata played no part in the maintenance of vascular tone and normal blood pressure. Yet STRÖM (1950 a) showed, as pointed out above, that centers in higher regions of the brain were not without significance relative to the continuous regulation of vasomotor tone. Using thermic and electrical stimulation, he studied the role of the anterior hypothalamus in the cutaneous circulation. In experiments similar to those reported here he reached the conclusion that in some cases of acute decerebration through the mesencephalon, there was a substantial though transient increase of blood flow in the cat's pads. In his opinion, those structures in the hypothalamus which served the heat regulation were of major importance to the level of tone in the vasoconstrictor nerves to the areas in question. The vasodilatation in the pads that attended decerebration was found, however, only in some experiments; in others the blood flow was not changed: "*If the spontaneous vasoconstrictor tone to the skin vessels was high, decerebration produced a great increase in cutaneous blood flow, lasting for many minutes. If the spontaneous vasoconstrictor tone was low, however, decerebration did not materially change the cutaneous blood flow.*" STRÖM did not study the localization of the descend-

ing pathway in the brain stem, wherefore it is difficult to judge its relation to the tectal vasoconstrictor neurons.

In short, it may accordingly be said that the results illustrate further the predominant significance of the medullary vasomotor centers relative to the continuous regulation of vascular tone in an anesthetized animal.

2. Influence of the Baroceptor Mechanisms on the Vascular Responses to Stimulation in the Mesencephalon

It has been pointed out in the foregoing that the vascular responses studied here were quite irregular insofar as the blood pressure was concerned. There was sometimes a rise, usually moderate, and sometimes a fall of blood pressure; in some experiments no changes were found at all. It is conceivable, of course, that in those cases where blood pressure variations did occur, reflexes via the baroceptor regions could have influenced the recorded peripheral responses, either amplifying or counteracting. That any of these responses could have been due solely to such reflexes seems implausible, however, having regard, for instance, to those peripheral responses of characteristic appearance that were not manifested in blood pressure variations (*cf.* Chapter II).

Many of the experiments described were performed on animals in which the baroceptor mechanisms had been functionally eliminated—by bilateral vagotomy and occlusion of both carotids, or bilateral denervation of the carotid sinus. This had no qualitative effect on the responses induced by mesencephalic stimulation. As regards the vasodilatation in skeletal muscles, the impression was gained that the increase of blood flow was often greater in animals with functionally eliminated baroceptor mechanisms. The explanation of this may lie in the generally higher vasoconstrictor tone and hence the higher vascular tone that prevail under such conditions.

With the aim of studying more carefully the significance of the baroceptor mechanisms, a few experiments were performed in which the responses to stimulation before and after elimination of

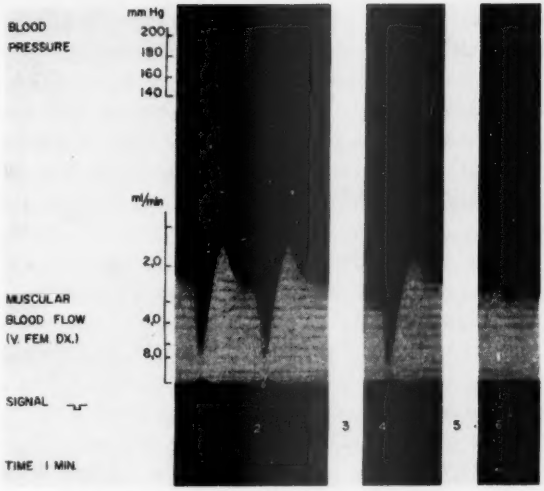


Fig. 52. Cat 2.4 kg. Dial 60 mg/kg. Nn. vagi cut. Artificial respiration. Vasodilator responses in the muscles of the right hind leg to stimulation in the right part of the tectum mesencephali before and after functional elimination of the sinus baroceptor mechanisms.

1. Stimulation, 2.5 V, 10 sec.
2. „ — „ „ „ „ „
3. Aa. carotides commun. occluded.
4. Stimulation, 2.5 V, 10 sec.
5. Atropine 0.2 mg/kg I.V.
6. Stimulation, 2.5 V, 10 sec.

Note the fall of blood pressure on stimulation after occlusion of the common carotids; the vasodilator response is uninfluenced.

those mechanisms were compared. The result of one such experiment is shown in figure 52. Bilateral vagotomy had been done at the outset. Repeated stimulation in the tectum mesencephali elicited a pronounced increase of flow in the muscles of the right hind leg. It will be noted specially that no changes of blood pressure occurred. It might be asked how this blood pressure balance was brought about. In the relevant experiment the blood flow was not recorded in any other vascular area than a muscular region, but numerous experiments reported earlier have shown the cutaneous and intestinal vasoconstriction attending vasodilatation in the muscles. For this reason the total peripheral resistance may not have been changed, so that the peripheral responses were not reflected in blood pressure phenomena. Nor, however, must the levelling effect of the sinus mechanisms be disregarded. When

these were eliminated by occlusion of both carotids (the baroceptors in the aortic region had already been eliminated at the outset), the blood pressure level rose from 140 mm to about 200 mm Hg. Evidently there had been a general increase of vasoconstrictor tone, i.e. in the skeletal muscles too; for notwithstanding the increased blood pressure the flow in the vascular area studied was only very slightly higher than before. Stimulation at the same point and with the same intensity as before, still produced a substantial increase of flow in the muscles. In addition there was a distinct fall of blood pressure, yet even so the increase of flow was greater than before.

Was this fall of blood pressure due solely to elimination of the buffer mechanisms? This, of course, played a role, but it should also be borne in mind that the high vasoconstrictor tone in fibers to e.g. skin and intestinal areas probably could have increased further only to a minor degree as a result of stimulation.—It may be mentioned that in some experiments stimulation nevertheless caused an increase of tone, reflected in a rise of blood pressure particularly after atropinization (see e.g. figure 28).—In view of this high vasoconstrictor tone, the blood pressure levelling mechanism constituted by concomitant increase of the vasoconstrictor impulses to the relevant vascular areas might therefore, to a large degree, have been put out of action. The vasodilatation in the muscles would thus have reduced the total peripheral resistance, and the fall of blood pressure was the visible evidence of this. After atropine, stimulation no longer had any effect on the blood flow, and hence caused no fall of blood pressure.

The results of this experiment suggest, in short, that the peripheral responses (at all events vasodilatation) to stimulation in the tectum mesencephali are quantitatively dependent on vasoconstrictor tone but are qualitatively independent of the baroceptor mechanisms.

It is more difficult by similar experiments to demonstrate univocally the independence of the vasoconstrictor component relative to the baroceptor mechanisms. As a result of the high vasoconstrictor tone following elimination of the baroceptors, the responses were often dominated by the vasodilatation and

fall of blood pressure. In view of this latter, it cannot be said with any assurance whether a decrease of flow in e.g. a cutaneous area is largely passive thereto, or is attributable to active vasoconstriction. One approach, however, is to study the conditions in atropinized animals in which vasodilatation and fall of blood pressure have been blocked. Several experiments showed that the vasoconstriction, for instance in the skin, induced by stimulation in the tectum mesencephali still persisted after atropine (see e.g. figures 11 and 28), both in cats with intact and in those with eliminated baroceptors. The vasoconstriction was usually manifested as a rise of blood pressure; in no case was there any fall that might conceivably have produced the decrease of flow hemodynamically or via baroceptor reflexes. The vasoconstrictor impulses to the skin and splanchnic region must be considered to be independent of the baroceptor mechanisms.

Comment

The present results are in accordance with those of earlier investigations that elucidated the problem of the existence of a functional relationship between the baroceptor mechanisms and the sympathetic vasodilator system, from a somewhat different point of view: Do sympathetic vasodilator nerves participate in baroceptor reflexes? The answer was in the negative and it was shown that vasodilatation occurring on activation of the baroceptors is caused by inhibition of the vasoconstrictor tone (Folkow and Uvnäs, 1948 b; Frumin, Ngai and Wang, 1953; Lindgren and Uvnäs, 1955).

The results show that the reaction pattern in activation of the mesencephalic vasomotor neurons is unchanged after elimination of the baroceptor mechanisms and independent of the level of the continuous vasoconstrictor tone. They indicate, too, that none of the observed components of the reaction pattern are due to those baroceptor mechanisms. However, these latter naturally function as usual in blood pressure variations induced by mesencephalic stimulation, and contribute to a quantitative modification of the peripheral responses.

3. Relation of Mesencephalofugal Vasomotor Pathways to Bulbar Vasoconstrictor and Vasodilator "Centers"

From the results reported in Chapter IV it was evident that the tectum mesencephali contains independent vasomotor neurons of different types. Various sympathetic components are represented there: vasodilator neurons to the muscles, vasoconstrictor neurons to cutaneous and intestinal areas, and excitatory neurons to the adrenal medulla. It was shown to be probable that the efferent vasodilator pathway passed the medulla oblongata without further synapses. The efferent fibers from the mesencephalon were located in the ventro-lateral part of the medulla oblongata, from which LINDGREN and UVNÄS (1953 b), in experiments on animals with intact brains, showed that sympathetic vasodilator nerves could be activated. They stated that the muscle vasodilatation was accompanied by vasoconstriction in skin and splanchnic areas. It was regarded as a result of direct activation of vasoconstrictor fibers running together with the sympathetic vasodilator fibers in the medulla oblongata. In principle, therefore, the reaction pattern seems to have resembled that induced by stimulation in the tectum mesencephali. As was pointed out above, too, there is good reason to believe that those efferent pathways of the different components which originate there, run in that circumscribed part of the medulla oblongata and are identical with the pathways studied by LINDGREN and UVNÄS.

These authors held that vasodilator responses to medullary stimulation were solely ipsilateral. They did not enter into any discussion of the distribution of the vasoconstrictor responses, but those in the experiments reported were ipsilateral.

In order to find out if the vasoconstrictor responses too were ipsilateral, the following type of experiment was conducted. The cat was prepared for stimulation in the medulla oblongata. The blood flow was recorded in three areas concurrently: in both hind paws and in the muscles of the right hind leg. The result of such an experiment is shown in figure 53. Stimulation was given in the medulla oblongata at the level of the oliva superior, 4 mm to the right of the midline and about 2 mm above the ventral surface. The result was characteristic vasodilatation in the

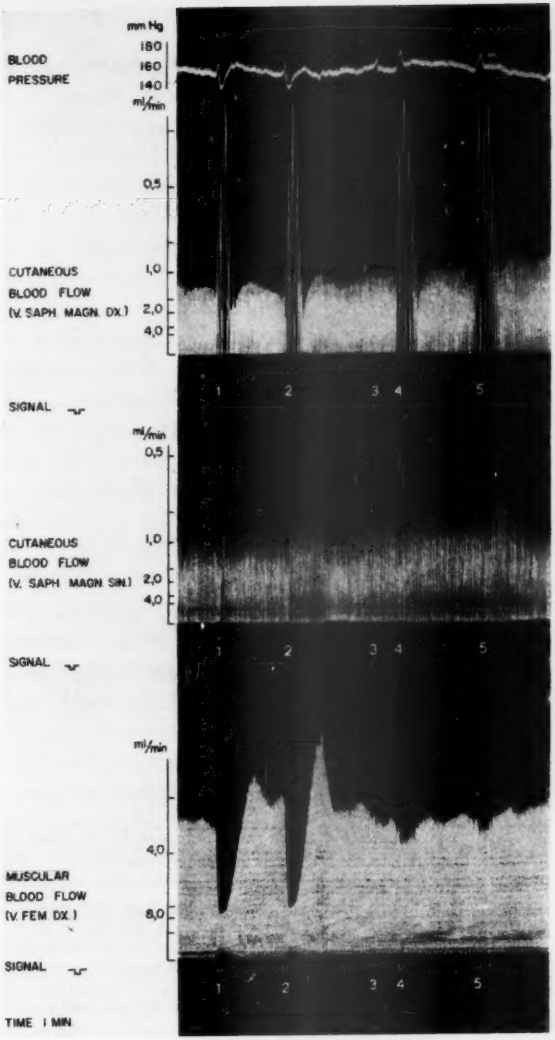


Fig. 53. Cat 3.2 kg. Dial 45 mg/kg.

Adrenals removed. Aa. carotides commun. occluded. Nn. vagi cut.

Vasoconstrictor responses in the skin of the right hind leg and vasodilator responses in the muscles of the same leg to stimulation of the sympathetic vasodilator pathway in the right part of the medulla oblongata.

1. Stimulation, 2.5 V, 10 sec.
2. „ — „ „ „ „ „
3. Atropine 0.2 mg/kg I.V.
4. Stimulation, 2.5 V, 10 sec.
5. „ — „ „ „ 15 „

Note that the vasoconstrictor responses in the skin accompanying the vasodilator responses in the muscles occurred only in the ipsilateral leg.

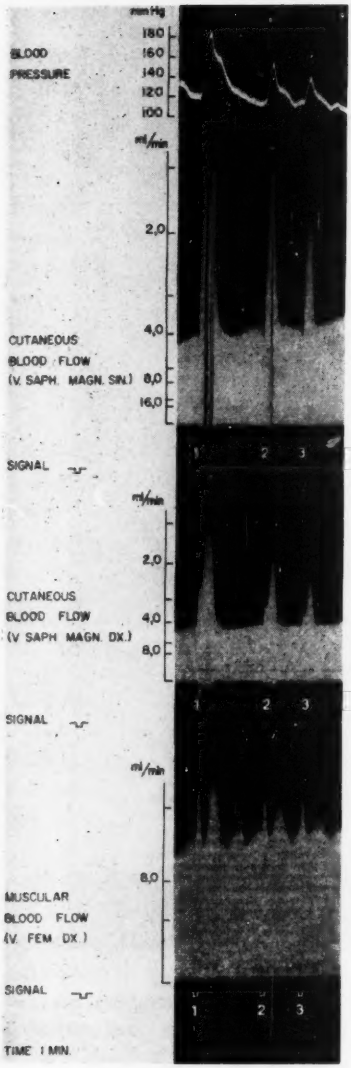


Fig. 54. Cat 3.0 kg. Dial 50 mg/kg. Adrenals removed. A. carotis commun. sin. occluded.

Vasoconstrictor responses in the skin of the left and right hind legs and in the muscles of the right hind leg to stimulation of the "vasoconstrictor center" in the fovea inferior in the right part of the medulla oblongata.

1. Stimulation, 2.0 V, 10 sec.
2. „ — „ 1.5 „ „ „
3. „ — „ 1.0 „ „ „

Note the bilateral distribution of vasoconstrictor responses to unilateral stimulation.

muscles. Considerable vasoconstriction occurred in the ipsilateral hind paw, but the blood flow from the contralateral paw showed no significant changes. The blood pressure response consisted of a negligible initial rise, followed by a slight decrease. The muscle vasodilatation was blocked as usual after atropine. The vasomotor reactions in the skin, on the other hand, were unchanged and gave rise to a slight rise of blood pressure.

For purposes of comparison similar experiments were performed with stimulation of another medullary structure, located more dorsally in the rhomboid fossa, the vasoconstrictor center. Stimulation of the vasoconstrictor center on the right side in the fovea inferior, 1-2 mm below the dorsal surface, produced, as shown in figure 54, pronounced bilateral vasoconstrictor responses in the skin (both hind paws), attended by a substantial rise of blood pressure. This notwithstanding, the muscle blood flow also diminished somewhat, suggesting vasoconstrictor involvement of that vascular area too, even though it was not so pronounced as that in the skin.

Having regard to the role of predominant central region for the vasomotor control, which this vasoconstrictor center in the medulla oblongata has earlier been accounted, these results are interesting. The most likely explanation of the different distributions of vasoconstrictor impulses to cutaneous vessels on stimulation in ventro-lateral parts of the medulla oblongata, compared with stimulation in the vasoconstrictor center, seems to be that the vasoconstrictor fibers from the mesencephalon pass the medulla oblongata without being connected with or relayed via that vasoconstrictor center. If this hypothesis were correct, then it would be possible to remove the whole of this area in the medulla oblongata, and vasoconstrictor impulses elicited from the mesencephalon would still be conducted.

With a view to studying this possibility, experiments of the following type were performed. (The result of one of them is shown in figure 57.) The cat was prepared for stimulation in the tectum mesencephali by opening the skull over the posterior lobes in the usual manner. In addition, the occipital bone and most of the cerebellum were removed in order to facilitate inspection of the medulla oblongata. To obviate any

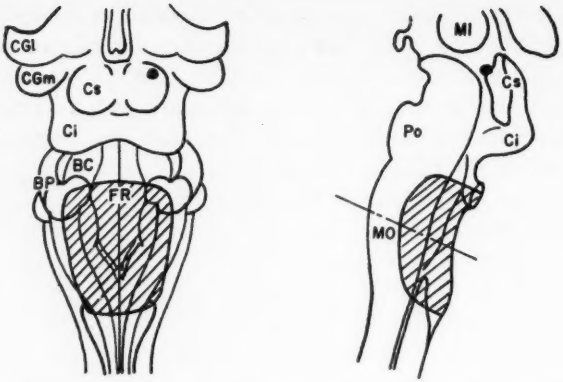


Fig. 55. Schematic drawings of the brain stem, dorsal and sagittal views, showing the extension of the cauterized area and localization of the mesencephalic stimulation point. The responses in this experiment are shown in fig. 57. The section through the medulla oblongata in the sagittal view indicates the level of the frontal section shown in fig. 56. (Scale 1.4: 1.)

effects from the adrenals, those organs were eliminated at the start of the experiment. Similarly, bilateral vagotomy was done in order to have the carotid sinuses on either side as the only baroceptor regions. Only the blood pressure was recorded. Stimulation in the tectum mesencephali produced comparatively large rises of blood pressure (1 and 2 in figure 57); in order to render these more distinct, 0.1 mg atropine per kg had been given at the start in order to block the vasodilator component. Occlusion of both carotids was used as a test of the integrity of the dorsal medullary vasomotor functions (vasomotor center).—This measure abruptly reduces the pressure in the carotid sinus, the normal inhibition of vasoconstrictor tone thus ceasing.—Bilateral occlusion of the carotids, as will be seen from 3, 4 and 5 in the figure, caused very pronounced rises of blood pressure. At 6 in the figure, bilateral cauterization was done of the dorsal structures of the medulla oblongata. The damaged tissues were removed by suction. The extent of the lesion, which involved the vasoconstrictor center and depressor area bilaterally as well as large adjacent zones, will be seen from figures 55 and 56. During the course of a few minutes thereafter the blood pressure fell to 80-60 mm Hg,

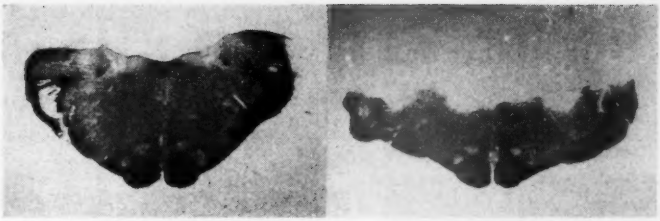


Fig. 56. Histological frontal sections through the medulla oblongata immediately anterior to the oliva inferior. The right section shows the non-removed parts at this level (the experiment is described in detail in figure 57); the left one is from a normal brain. (Scale 2.5: 1.)

the initial level having been 140 mm Hg. Occlusion of the carotids still produced a very slight pressor effect (7 and 8 in the figure). This could naturally have been a result of nervous vasoconstrictor activity, but another possible explanation is that when the arteries to the head were occluded the entire cardiac output was suddenly distributed to other parts of the body, thus raising the pressure somewhat. When the occlusion was effected less abruptly, during the course of 5-10 seconds, the slight rise of blood pressure (no. 9) did not appear.

Yet further stimulation in the tectum mesencephali still produced a rise (nos. 10 and 11), showing that the neurons mediating these impulses were located in the ventral parts of the medulla oblongata and had no connection with the dorsal tone-regulating centers. One proof that the cauterization of the tone-regulating structures was complete—i.e. that the loss of centrally induced vasoconstrictor tone was total—is that section of the spinal cord at first cervical level did not reduce the blood pressure further. The experiment suggests, too, that vasoconstrictor neurons from the mesencephalon or structures located higher were non-tonic.

Comment

Most workers appear to hold the view that vasomotor responses produced via higher regions—the cortex, hypothalamus, and mesencephalon—are bilateral. As to the medulla oblongata, however, opinions are more divided.

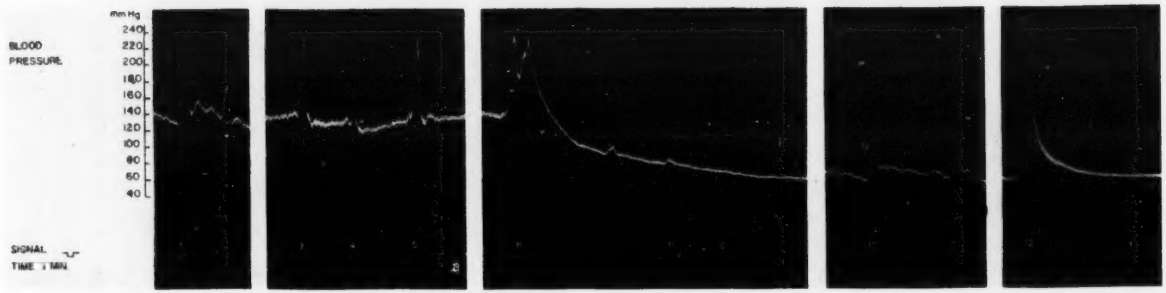


Fig. 57. Cat 3.1 kg. Dial 40 mg/kg. Adrenals removed. Nn. vagi cut. Atropine 0.1 mg/kg I.V.
Blood pressure responses to occlusion of the common carotids and to stimulation in the right part of the tectum mesencephali before and after cauterization of the dorsal parts of the medulla oblongata including the "vasomotor centers" on both sides. The extension of the cauterization is seen in figs. 55 and 56.

1. Stim. in the mesencephalon, 4.0 V, 20 sec.
2. „ „ „ „ — „ 3.0 „ 15 „
3. Occlusion of aa. carotides commun., 30 sec.
4. „ „ „ „ „ 15 „
5. „ „ „ „ „ 30 „
6. Cauterization. Artificial respiration.
7. Occlusion of aa. carotides commun., 30 sec.
8. „ „ „ „ „ 60 „
9. „ „ „ „ „ 60 „
10. Stim. in the mesencephalon, 4.0 V, 20 sec.
11. „ „ „ „ — „ 3.0 „ 15 „
12. Section of the spinal medulla at C_1.

Note that the pressor responses due to occlusion of the common carotids disappeared after cauterization of the "vasomotor centers" but those due to mesencephalic stimulation remained. Section below the medulla oblongata did not lower the blood pressure more than cauterization had done.

As regards the medullary portion of the sympathetic vasodilator fibers, available reports are in agreement that unilateral activation produces ipsilateral vasodilatation in the skeletal muscles. Bearing this in mind, it is not surprising that the accompanying vasoconstrictor fibers have also been found to have only an ipsilateral distribution. Since stimulation in another region of the medulla oblongata induced both ipsilateral and contralateral vasoconstriction in the skin, the conclusion can scarcely be other than that there are two different efferent vasoconstrictor pathways in and from the medulla oblongata.

The bilateral response to activation of medullary structures is doubtless the commonest. This applies, at all events, to the following three types:

Vasoconstrictor center. The effects of stimulation of the region round the fovea inferior were carefully investigated by CHEN, LIM, WANG and YI (1936). Unilateral stimulation produced bilateral vasoconstriction in the kidneys, bilateral mydriasis, contraction of both nictitating membranes, and mostly bilateral vasoconstriction in the extremities (in some cases this latter was only ipsilateral). The same authors, in a further paper (1937 c) reported that the partial decussation of the efferent pathways from the vasoconstrictor centers of either side was located at spinal level, caudal to the second cervical segment. HARRISON, WANG and BERRY (1939) arrived at similar results.

Depressor area. Unilateral stimulation of the depressor area invariably produces bilateral inhibition of vasoconstrictor tone (LINDGREN and UVNÄS 1954 a).

Baroceptor reflexes. These reflexes, too, are effected to both sides. For instance, unilateral afferent stimulation of a sinus or vagus nerve serves to inhibit vasoconstrictor tone in both hind legs (e.g. LINDGREN and UVNÄS, 1955).

These three mechanisms can probably be regarded as a functional entity, even though the detailed neuronal relationships are not fully elucidated. Characteristic, too, is that a small lesion of these dorsal structures in the medulla oblongata often affects more than one of the mechanisms. LINDGREN and UVNÄS (1954 a) thus reported that cauterization of the depressor area blocked de-

pressor responses to stimulation of the sinus and vagus nerves. SUH, WANG and LIM (1936) recorded similar findings in cauterization of the pressor region.

The experiments undertaken here, with removal of these dorsal regions leaving only the most ventral parts of the medulla oblongata—whereby the mesencephalofugal vasoconstrictor pathway was shown to be intact—also support the view that two separate vasoconstrictor pathways exist as far down as spinal level. How these pathways run in relation to each other after the first to second cervical level is not known; probably they both run in the ventrolateral column. It has been observed, at all events, that vasoconstrictor pathways from both the hypothalamus (WANG and RANSON, 1939 b) and the vasoconstrictor center in the medulla oblongata (CHEN, LIM, WANG and YI, 1937 c) have that course.

The medullary organization of those vasoconstrictor neurons to skin and splanchnic area which accompany the sympathetic vasodilator fibers seems, accordingly, to be analogous with that of the latter. As regards the vasodilator neurons, LINDGREN and UVNÄS (1955) maintained that they had no anatomic or functional connection with the dorsal medullary vasomotor system.

Discussion

The results, in short, point to the existence of separate vasomotor "centers" in the mesencephalon and medulla oblongata, fully differentiated anatomically, with separate efferent pathways running directly to spinal neurons, and probably with different functions. Some authors have expressed similar views with regard to the relation between hypothalamus and medulla oblongata in the vasomotor sense. WANG and RANSON (1939 b), for instance, discussing the location of the hypothalamofugal pathways in the medulla oblongata, wrote: "*It is reasonable to assume that in the periventricular gray of the floor of the fourth ventricle (about 2.5 mm in depth) there is a region from which pressor responses are elicitable but which differs from the lateral*

reticular formation in its relation to the hypothalamus; the former being the semi-independent reflex vasomotor center and the latter constituting the main hypothalamic efferent pathway."

The mesencephalo-spinal tract studied here (as a continuation of the cortico-hypothalamo-mesencephalic portion of the same pathway) must not of course, where pressor fibers are concerned, be regarded as the only, or even the main, descending connection from supramedullary parts of the brain. On the contrary, it was possible to verify earlier findings that such neurons are diffusely scattered over large parts of the brain stem. They probably include some neurons that produce pressor responses by running to the vasoconstrictor center in the medulla oblongata; others perhaps extend to spinal level.

THOMPSON and BACH (1950), in contrast to WANG and RANSON (1939 b), asserted that hypothalamic vasomotor impulses were chiefly effected via the bulbar vasomotor center. Electrical stimulation in the posterior hypothalamus or anterior mesencephalon in cats elicited both pressor and depressor reactions. Circumscribed lesions of the lateral and of the medial reticular formation in the medulla oblongata reduced or blocked the effects. However, the lesions were fairly discrete and could not possibly have involved the whole area constituting the vasomotor center. It is conceivable that some hypothalamo-spinal connections were interrupted, too.

It is probable that as regards hypothalamo-mesencephalofugal vasoconstrictor fibers there are different pathways with different bulbar localizations and organizations. The question now arises: What is the function of those hypothalamofugal excitatory and inhibitory neurons that run to the vasomotor center? The bulbar vasomotor tone, reflexes, etc. are considered, as is known, to persist after interruption of connections from higher regions of the brain. As has emerged, for instance, from the results presented here, the aforementioned pathways are probably non-tonic and of no importance to the level of vascular tone in anesthetized animals, any more than other hypothalamo-mesencephalofugal pathways (aside from those fibers that serve the thermoregulation).

For further comment on the functional significance of the sympathetic vasodilator system and its vasoconstrictor and adreno-medullary components, reference should be made to the general discussion.

Summary and Conclusions

The anatomic and functional relation of the tectal vasomotor neurons to the bulbar vasomotor center was investigated in acute experiments. The effect of section of the tectofugal vasodilator and vasoconstrictor pathways on the blood flow in muscles and skin was studied, and likewise the influence of the baroceptor mechanisms on responses to stimulation. Attention is drawn to the unilateral distribution of the ventro-lateral tectofugal vasomotor pathway, compared with the bilateral responses from the vasoconstrictor center and the depressor area. In other experiments the transmission of vasomotor impulses from the mesencephalon was investigated after destruction of those bulbar regions.

The following conclusions are drawn.

1. The mesencephalic vasodilator and vasoconstrictor neurons have no significance relative to the continuous maintenance of vascular tone in the muscles and skin of anesthetized cats; i.e., they probably have only very slight basal activity or none at all. Vascular tone is maintained by the medullary vasomotor center.

2. The vascular responses to stimulation in the tectum mesencephali are qualitatively independent of the baroceptor reflexes.

3. The tectofugal vasodilator and vasoconstrictor pathways are anatomically and functionally separate from the vasoconstrictor center and the depressor area in the medulla oblongata.

CHAPTER VI

General Discussion

"The question arises as to the role of the sympathetic centres in the hypothalamus and myelencephalon . . . . .

"Whether the hypothalamic discharges act directly on the spinal sympathetic (preganglionic) cells or whether they are relayed via the myelencephalic neurones, we do not know . . . . .

"Thus it is suggested that 'postural sympathetic reflexes' are mediated through the myelencephalic centre, while 'emotional sympathetic reactions' are aroused through the hypothalamic centre." (LIM, 1938)

Even though the commonest view is probably that vasomotor regions in different parts of the brain directly constitute, in the functional sense, higher or lower links, as the case may be, in one and the same chain, the idea is evidently not new that the central nervous system contains different vasomotor systems having separate centers, separate efferent pathways and separate functions. In accordance with the hypothesis quoted above, a distinction has therefore been made between the hypothalamic and the medullary system. The discussion has usually concerned the whole of the sympathetic nervous system with its various components. As regards the vasomotor component it has concerned only different vasoconstrictor centers and pathways and sometimes vasoconstrictor-inhibitory ones—for central sympathetic vasodilator neurons have been known only for a few years.

Such hypotheses of separate intracerebral sympathetic pathways are supported both by earlier findings and by the present observations as to the sympathetic vasodilator system with special reference to its intracerebral localization and functional relation to the medullary vasomotor apparatus. The results reported in Chapter V regarding the organization of those vasoconstrictor neurons which

accompany the sympathetic vasodilator pathway, also lend considerable weight to LIM's theory. The fact that the mesencephalon, and not the hypothalamus, probably constitutes the most caudal relay station for these vasoconstrictor neurons does not alter the principle of the theory. The most important corollary seems to be that these vasoconstrictor fibers and those running from the vasoconstrictor center in the medulla oblongata converge at spinal level; probably both groups run to the same preganglionic cells in the lateral horn. The organization of these autonomic pathways would thus be analogous with that existing in the somatic system and the preganglionic neurons would constitute what, in the latter system, SHERRINGTON called "the common final path".

Whether there exist, in addition to these two, other vasoconstrictor pathways converging at spinal level is not known. That such is the case does not seem inconceivable: in both the hypothalamus and the mesencephalon pressor reactions can be elicited from entirely different regions than those representing the sympathetic vasodilator pathway—and only some of these reactions are likely to be effected via the vasomotor center in the medulla oblongata. The efferent pathways from the thermoregulating center in the hypothalamus must also be considered. Different vasoconstrictor areas with separate efferent pathways, at all events in the upper part of the brain stem, have been found in the cortex (HUNSICKER and SPIEGEL, 1934; SPIEGEL and HUNSICKER, 1936; GREEN and HARTZELL, 1938; WALL and DAVIS, 1951).

By comparison with the vasoconstrictor neurons the sympathetic vasodilator pathway presents a fairly simple structure. Its neuronal organization does not seem to be very complicated, cortex—hypothalamus—mesencephalon, with the mesencephalic neurons probably running to preganglionic sympathetic vasodilator neurons in the lateral horn. In figure 58 is a schematic representation of the probable central and peripheral extension of this pathway.

In what functions, then, are the two nervous systems involved? What reflexes and other nervous manifestations are mediated via the centers in the medulla oblongata, exciting or inhibiting the preganglionic vasoconstrictor neurons distributed to all tissues, and which of them are relayed via the cortex, hypothalamus

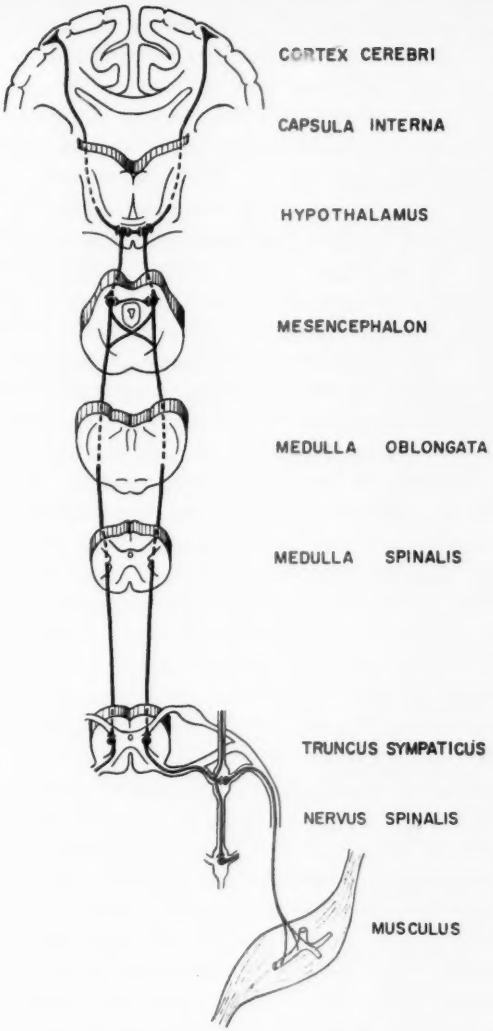


Fig. 58. Schematic drawing showing the central and peripheral extension of the sympathetic vasodilator pathways.

or mesencephalon to vasodilator neurons to skeletal muscles and vasoconstrictor neurons to skin and viscera?

Reflexes via the first-named system are well known. Impulses from the baroceptors occur both at rest and during exercise. Whether these afferent impulses directly inhibit the tonic activity of the medullary vasoconstrictor center or, via a medullary inhibitory center, inhibit at spinal level does not seem to be fully elucidated. That the latter mechanism at least occurs was shown by LIM, WANG and YI (1938), YI (1938) and by ALEXANDER (1946). Further, CHEN, LIM, WANG and YI (1937 a) demonstrated that pressor reflexes, with spinal nerves (brachial and ischiatic) as afferent pathways, are relayed via the vasoconstrictor center. The medullary centers also received facilitating and inhibitory impulses from higher centers, e.g. the hypothalamus (THOMPSON and BACH, 1950). The implications of this are but little known, however.

Several authors investigating medullary vasomotor reflexes—depressor ones—have specially sought possible activation of cholinergic sympathetic vasodilator fibers as the efferent link. FOLKOW and UVNÄS (1948 b) demonstrated that vasodilator responses to baroceptor activity or to afferent stimulation of a peripheral nerve (brachial) were not brought about via those fibers. Similar results were presented by FRUMIN, NGAI and WANG (1953) as regards activation of the carotid sinus or the aortic arch baroceptors. They wrote: "*It is concluded that the only mechanism for eliciting dilatation through medullary reflexes is inhibition of sympathetic constrictor discharge.*"

As regards the function of the sympathetic vasodilator system our knowledge is very imperfect; virtually nothing is known of the activity in its central part under physiologic conditions. If coincident activation of the various components were the case, it would assuredly be appropriate in some situations. A redistribution of the circulating blood volume from skin and viscera to skeletal muscles creates optimal conditions for muscular work. Numerous investigations have demonstrated that these phenomena may indeed occur. For instance, HERRICK, GRINDLAY, BALDES and MANN (1940) found that the blood flow increased two- to ten-fold in the hind legs of running dogs but was unchanged in the viscera even though the blood pressure rose. Experiments on human

beings have shown, in the initial stage of muscular exercise, such rapid changes in the circulation (cutaneous vasoconstriction, increase of minute volume) that they must be attributed to nervous regulation (KROGH and LINDHARD, 1913; ASMUSSEN, CHRISTENSEN and NIELSEN, 1940; CHRISTENSEN and NIELSEN, 1942). Quite recently HOLMGREN (1955) showed that even the first heart beat at the start of muscular exercise presented a shortening of diastole, and during the course of the first ten seconds there was a minor, though characteristic blood pressure variation consisting of a slight rise, a transient fall, and then a further rise. Even though such circulatory changes do not necessarily involve vasodilator impulses to the muscles—FLEISCH (1929, 1932), for example, did not believe in such a phenomenon—they nevertheless have to be regarded as the results of cortical activity. LUND (1947) believed that the cutaneous vasoconstriction was due to impulses from the motor cortex concurrently with the somatomotor impulses, but was inclined to attribute the initial muscle vasodilatation to reflexes resulting from elevated blood pressure. It is remarkable, however, to note the localization of cortical sympathetic vasodilator neurons in the motor area (ELIASSON, LINDGREN and UVNÄS, 1952)—a finding that may suggest coincident activation of those and of somatic motor neurons.

Although supramedullary vasomotor functions probably play an important role in muscular work, at all events in the early stages of it, the medullary mechanisms such as the baroceptor ones must not be forgotten. EULER and LILJESTRAND (1946), experimenting on cats and dogs, found that muscular work induced a substantial fall in blood pressure after denervation of both sinus regions and bilateral vagotomy, whereas the same rate of work did not alter the blood pressure in normal animals. They used anesthetized animals, however, and the muscular contractions were due to electrical stimulation of spinal cord or peripheral nerves. Therefore, conclusions can scarcely be drawn as to the significance of supramedullary vasomotor impulses attending motor activity.

It would seem natural for the sympathetic vasodilator system (with the relevant vasoconstrictor nerves to other vascular areas

and excitatory nerves to the adrenals) to be involved in states of sudden effort. That the adrenals are stimulated in fright reactions was already shown, in the cat and dog, by CANNON and DE LA PAZ (1911). Such conditions—emergency states—were further studied, particularly with respect to the autonomic components, by CANNON and his associates (*vide* e.g. CANNON, 1928; CANNON and ROSENBLUETH, 1937). Those authors found them to be characterized by mass activation of the sympathetic nervous system. The hypothalamus was regarded as an integrative region in these discharges (BARD, 1928). Whether sham rage reactions, for example, are associated with a discharge even in sympathetic vasodilator neurons is not known but does not seem unlikely; the hypothesis was already propounded when the hypothalamic representation of those neurons was demonstrated (ELIASSON, FOLKOW, LINDGREN and UVNÄS, 1951).

By exteriorizing of a small area of colonic mucosa the vascular reactions therein can be directly observed under varying conditions. DRURY, FLOREY and FLOREY (1929), studying dogs treated in this way, observed that fright was associated with abrupt pallor of the colonic mucosa with a latency of 4-5 seconds, suggestive of pronounced vasoconstriction. The same reaction appeared in an adrenalectomized animal. Similar visceral vasoconstriction was also observed initially in connection with sudden muscular effort (BARCROFT and FLOREY, 1929).

Such experiments naturally afford no clue as to the intracerebral pathways of the vasomotor impulses; they merely indicate that cerebral regions are involved.

In experiments on human beings, BARCROFT and his associates (BARCROFT, EDHOLM, MCMICHAEL and SHARPEY-SCHAFER, 1944; BARCROFT and EDHOLM, 1945) reached the conclusion that sympathetic vasodilator fibers to the skeletal muscles were activated in posthemorrhagic syncope. The actual mechanism and detailed reflex arc are unknown. Syncope is generally associated with marked pallor, and cutaneous vasoconstriction can usually be recorded objectively with a plethysmographic method (BARCROFT, EDHOLM, 1945). SNELL, CRANSTON and GERBRANDY (1955), however, by measuring the heat loss from the hand were able to demonstrate the opposite reaction in syncope, i.e., cutaneous

vasodilatation. It seems difficult, therefore, to draw any definite conclusions regarding the vasomotor reactions associated with this phenomenon.

What, then, is the function of the mesencephalic relay station of the sympathetic vasodilator system? Are there any reflexes that are relayed, via that station, to sympathetic vasodilator and vasoconstrictor neurons? Although this problem is still obscure, there are abundant prerequisites for the existence of such reflexes. Both the tectum and the tegmentum mesencephali have a complicated nuclear pattern and numerous afferent connections (HUBER, CROSBY, WOODBURNE, GILLILAN, BROWN and TAMTHAI, 1943; BUCHER and BÜRGI, 1950; MARBURG and WARNER, 1947). A number of cortico-tectal and cortico-tegmental pathways exist; fibers run from various parts of the hypothalamus—not merely the portion of the sympathetic vasodilator pathway that is described here. Further, there are spino-tectal and bulbo-tectal pathways, the latter including important cochlear and vestibular pathways; and, not least, the optic pathway with direct retino-tectal as well as pregeniculo-tectal and occipito-tectal fibers.

The numerous afferent and efferent connections to and from this part of the brain are illustrated by the complex pain reactions (crying, struggling, flight or defense reactions) elicitable by electrical stimulation in the tectum mesencephali in conscious cats (SPIEGEL, KLETZKIN and SZEKELY 1954). WALKER (1943), too, suggested that the tectum mesencephali represents an integrative region for pain reactions—actually the lowest level for them. In view of the activation of both somatic and autonomic efferent neurons that often attends alarm states, it is not unlikely that such mesencephalic pain reactions will also involve vasomotor neurons.

Using various physiologic stimuli (activity of the animal, pulling and rubbing the skin) KELLER (1932) studied the responses in chronic mid-brain preparations (cats). He observed constriction of the pupils, constriction of ear vessels, secretion of adrenaline from the adrenals and unco-ordinated motor effects. Although the hypothalamus was considered to play an important role in the intact animal, he concluded that "*the discharging of a typical*

rage response is not dependent on the brain-stem cephalad to the middle level of the mid-brain."

Activation of the adrenals is known to take place in various states of generalized activity, for instance in emergency states. An increase in adreno-medullary secretion during physical exercise has been shown by various workers. In man, EULER and HELLNER (1952) showed an increase in the urinary output of catechol amines in heavy muscular work. The ratio between adrenaline and noradrenaline was generally the same as at rest. Which nervous pathways are involved in such conditions is, of course, far from clear.

In the section dealing with the adrenal role in the reaction pattern studied here, it was pointed out that the adrenal medulla was usually activated but that the increase of the catechol secretion was so low that its effects on the blood flow in the muscles and skin were of minor importance compared to the nervous components. It is interesting to note that the humoral adrenal medullary component is also a feature of the reaction pattern in activation of the medullary vasomotor system, and even there is quantitatively insignificant. CHEN, LIM, WANG and YI (1937 a), commenting on stimulation in the vasoconstrictor center, wrote: "*Experiments on the role of adrenal secretion in the visceral response to central stimulation have further shown that the nervous factor accounts for the first and greater part of the response.*" This is fully consistent with the results of CELANDER's detailed studies of the adrenal medullary role in vascular reactions as compared with the direct sympathetic innervation (CELANDER, 1954).

In view of the partially different characteristics of the two catechol amines, adrenaline and noradrenaline, it would have been interesting to know their relative proportions in stimulation of the vasoconstrictor center and in stimulation of the sympathetic vasodilator pathway. Unfortunately such determinations were not possible in the present investigation; it was merely established that in mesencephalic stimulation an appreciable part of the total catechols consisted of adrenaline. EULER and FOLKOW (1953) reported a figure of 72 per cent noradrenaline in occlusion of the carotids, which finding can probably be regarded as tant-

amount to activation of the medullary vasoconstrictor center. According to KAINDL and EULER (1951) the percentage of noradrenaline in occlusion of the carotids is about the same as under resting conditions. An example of supramedullary activation of the adrenal medulla is the hypothalamic stimulation performed by BRÜCKE, KAINDL and MAYER (1952). They found an increase of adrenaline from the resting value of 11 per cent to about 50 per cent of the total catechols. These results may suggest yet another difference between medullary and supramedullary sympathico-adrenal discharges, and possibly between the two vasomotor systems; and this would thus be consistent with above-mentioned remarks on discrepancies in function.—However, the problem is fairly complex; it should be noted that hypothalamic stimulation may cause selective increase of the noradrenaline secretion, too (REDGATE and GELLHORN, 1953; FOLKOW and EULER, 1954).—Bearing in mind the purely vasoconstrictor properties of noradrenaline, the activity of the medullary vasoconstrictor center would most effectively be supported if that substance were the predominant factor, whereas adrenaline would best fit into the other reaction pattern, with vasodilatation in the skeletal muscles and vasoconstriction in other tissues. Having regard to the other effects of adrenaline in the organism, it is a considerably better "emergency hormone" than noradrenaline.

According to observations reported in earlier investigations and to the results presented and discussed here, the various neurons which, when activated, produce the reaction pattern of vasodilatation in skeletal muscles and vasoconstriction in skin and viscera apparently constitute not only an anatomical entity with a well-defined pathway in the brain-stem, but also a functional entity. It may be activated in various states of somatic activity.

Similarly, all components of the medullary vasomotor system (centers as well as afferent and efferent pathways, excitatory and inhibitory), which chiefly has a blood pressure controlling function, can be regarded as a functional entity.

The two systems seem to be anatomically as well as functionally separate from each other.

CHAPTER VII

General Summary

Previous investigations into nervous vasomotor control are briefly reviewed, with special reference to those bearing upon the role of different regions in the central nervous system.

In the present investigation cats were used. With the animals under Dial anesthesia, electrical stimulation was given in the mesencephalon as well as in the hypothalamus and medulla oblongata, with the Horsley-Clarke technique, and the venous blood flow was studied in skeletal muscles, skin and intestines.

Cholinergic sympathetic vasodilator nerves to the skeletal muscles were activated from a region in the tectum mesencephali, with coincident activation of vasoconstrictor nerves to skin and viscera and excitatory fibers to the adrenal medulla. This tectal region is the most caudal intracerebral relay station in the sympathetic vasodilator pathway, cortex—capsula interna— hypothalamus (relay station)—mesencephalon (relay station)—medulla oblongata—spinal medulla (relay to preganglionic neurons).

This vasodilator system, with accompanying vasoconstrictor fibers and adrenal medullary activating fibers, seems to have no direct relationship to the medullary vasomotor system. The efferent vasoconstrictor fibers of the two systems probably do not converge before reaching preganglionic cells in the lateral horn of the spinal medulla.

Various details of the results are discussed in the light of earlier literature. Conceivable physiologic functions of the cortico-hypothalamo-mesencephalic vasomotor system associated with different types of muscular activity are discussed and compared with known physiologic phenomena in which the medullary vasomotor center system is involved. The two systems are considered to have different main functions and are regarded as both anatomically and functionally separate.

REFERENCES

ALEXANDER, R. S., J. Neurophysiol. 1946. *9*. 205.

ALLEN, W. F., Amer. J. Physiol. 1931. *98*. 344.

ASMUSSEN, E., CHRISTENSEN, E. H., and NIELSEN, M., Skand. Arch. Physiol. 1940. *83*. 181.

BACH, L. M. N., Amer. J. Physiol. 1946. *145*. 474.

BACH, L. M. N., Amer. J. Physiol. 1952. *171*. 417.

BACQ, Z. M., Ann. Physiol. Physicochim. biol. 1934. *10*. 467.

BARCROFT, H., and EDHOLM, O., J. Physiol. 1945. *104*. 161.

BARCROFT, H., EDHOLM, O., MCMICHAEL, J., and SHARPEY-SCHAFER, E. P., Lancet. 1944. *1*. 489.

BARCROFT, H., and SWAN, H. J. C., Sympathetic control of human blood vessels. London. 1953.

BARCROFT, J., and FLOREY, H., J. Physiol. 1929. *68*. 181.

BARD, PH., Amer. J. Physiol. 1928. *84*. 490.

BAYLISS, W. M., J. Physiol. 1901. *26*. 173.

BAYLISS, W. M., J. Physiol. 1902. *28*. 276.

BAYLISS, W. M., J. Physiol. 1908. *37*. 264.

BAYLISS, W. M., The vasomotor system. London. 1923.

BEATTIE, J., Canad. med. Ass. J. 1932. *26*. 400.

BEATTIE, J., BROW, G. R., and LONG, C. N. H., Proc. Roy. Soc. 1930 a. *106 B*. 253.

BEATTIE, J., BROW, G. R., and LONG, C. N. H., Res. Publ. Ass. nerv. ment. Dis. 1930 b. *9*. 295.

BECHTEREW, W., Die Funktionen der Nervenzentra. Jena. 1908, 1909, 1911. Vol. I. II, III.

BECHTEREW, W., and MISSLAWSKY, N., Neurol. Zbl. 1886. *5*. 193.

BERRY, C., MCKINLEY, W., and HODES, R., Amer. J. Physiol. 1942. *135*. 338.

BOWEN, R. J., COOMBS, H. C., and PIKE, F. H., Proc. Soc. exp. Biol., N. Y. 1922. *19*. 181.

BRAUNER, F., BRÜCKE, F., KAINDL, F., and NEUMAYR, A., Arch. int. Pharmacodyn. 1951. *85*. 419.

BRONK, D. W., PITTS, R. F., and LARRABEE, M. G., Res. Publ. Ass. nerv. ment. Dis. 1939. *20*. 323.

BROOKS, C. M., Amer. J. Physiol. 1933. *106*. 251.

BROWN, G. L., and MAYCOCK, W. A., J. Physiol. 1940. *97*. 273.

BROWN, T. G., and SHERRINGTON, C. S., Quart. J. exp. Physiol. 1911. *4*. 193.

BRUSTEIN, S., Obošrên. psihiatr. 1901. Quoted from BECHTEREW, 1908.

Brücke, F., Kaindl, F., and Mayer, H., Arch. int. Pharmacodyn. 1952. *88*. 407.
Brücke, F., Loudon, M., and Werner, G., Z. KreislForsch. 1951. *40*. 513.
Bucher, V. M., and Bürgi, S. M., J. comp. Neurol. 1950. *93*. 139.
Burn, J. H., J. Physiol. 1932. *75*. 144.
Burn, J. H., Physiol. Rev. 1938. *18*. 137.
Bülbring, E., and Burn, J. H., J. Physiol. 1935. *83*. 483.
Bülbring, E., and Burn, J. H., J. Physiol. 1936 a. *86*. 61.
Bülbring, E., and Burn, J. H., J. Physiol. 1936 b. *87*. 254.
Bülbring, E., and Burn, J. H., J. Physiol. 1936 c. *88*. 341.
Cajal, S. R. y, Degeneration and regeneration of the nervous system. London. 1928.
Cannon, W. B., Ergebn. Physiol. 1928. *27*. 380.
Cannon, W. B., and de la Paz, D., Amer. J. Physiol. 1911. *28*. 64.
Cannon, W. B., and Rapport, D., Amer. J. Physiol. 1921. *58*. 338.
Cannon, W. B., and Rosenblueth, A., Autonomic neuro-effector systems. New York. 1937.
Cannon, W. B., and Rosenblueth, A., The supersensitivity of denervated structures. New York. 1949.
Celander, O., Acta physiol. scand. 1954. *32*. Suppl. 116. 132.
Celander, O., and Folkow, B., Acta physiol. scand. 1951. *23*. 64.
Chen, M. P., Lim, R. K. S., Wang, S. C., and Yi, C. L., Chin. J. Physiol. 1936. *10*. 445.
Chen, M. P., Lim, R. K. S., Wang, S. C., and Yi, C. L., Chin. J. Physiol. 1937 a. *11*. 355.
Chen, M. P., Lim, R. K. S., Wang, S. C., and Yi, C. L., Chin. J. Physiol. 1937 b. *11*. 367.
Chen, M. P., Lim, R. K. S., Wang, S. C., and Yi, C. L., Chin. J. Physiol. 1937 c. *11*. 385.
Christensen, E. H., and Nielsen, M., Acta physiol. scand. 1942. *4*. 162.
Christian, P., Arch. KreislForsch. 1954. *21*. 174.
Clark, G. A., J. Physiol. 1930. *69*. 171.
Clark, G. A., J. Physiol. 1934. *80*. 429.
Clarke, R. H., Johns Hopk. Hosp. Rep. 1920. Spec. Vol. 1.
Clementz, B., and Ryberg, C.-E., Acta physiol. scand. 1949. *17*. 339.
Crosby, E. C., and Henderson, J. W., J. comp. Neurol. 1948. *88*. 53.
Crosby, E. C., and Woodburne, R. T., J. comp. Neurol. 1951. *94*. 1.
Dale, H. H., J. Physiol. 1906. *34*. 163.
Dale, H. H., J. Physiol. 1913. *46*. 291.
Dale, H. H., J. Physiol. 1934. *80*. 10 P.
Danilewsky, B., Pflüg. Arch. ges. Physiol. 1875. *11*. 128.
Dastre, A. F., and Morat, J. P., C. R. Acad. Sci. Paris. 1880 a. *91*. 393.
Dastre, A. F., and Morat, J. P., C. R. Acad. Sci. Paris. 1880 b. *91*. 441.
Dittmar, C., Ber. Verh. sächs. Ges. Wiss. (Math.-Phys. Kl.), 1870. *22*. 18.
Dittmar, C., Ber. Verh. sächs. Ges. Wiss. (Math.-Phys. Kl.), 1873. *25*. 449.
Dole, V. P., Jr., and Morison, R. S., Amer. J. Physiol. 1940. *130*. 304.

Drury, A. N., Florey, H., and Florey, M. E., J. Physiol. 1929. *68*. 173.
Dunér, H., Acta physiol. scand. 1953. *28*. Suppl. 102.
Dusser de Barenne, J. G., and Kleinknecht, F., Z. Biol. 1924. *82*. 13.
Eckhard, C., Beitr. Anat. Physiol. 1873. *7*. 81.
Eliasson, S., Folkow, B., Lindgren, P., and Uvnäs, B., Acta physiol. scand. 1951. *23*. 333.
Eliasson, S., Lindgren, P., and Uvnäs, B., Acta physiol. scand. 1952. *27*. 18.
Eliasson, S., Lindgren, P., and Uvnäs, B., Acta physiol. scand. 1954. *31*. 290.
Elliott, T. R., J. Physiol. 1912. *44*. 374.
Emmelin, N., Acta physiol. scand. 1941. *2*. 289.
Erici, I., and Uvnäs, B., Acta physiol. scand. 1952. *25*. 10.
Euler, U. S. v., Acta physiol. scand. 1946 a. *11*. 168.
Euler, U. S. v., Acta physiol. scand. 1946 b. *12*. 73.
Euler, U. S. v., Pharmacol. Rev. 1951. *3*. 247.
Euler, U. S. v., and Folkow, B., Arch. exp. Path. Pharmak. 1953. *219*. 242.
Euler, U. S. v., and Gaddum, J. H., J. Physiol. 1931. *73*. 54.
Euler, U. S. v., and Hellner, S., Acta physiol. scand. 1952. *26*. 183.
Euler, U. S. v., and Liljestrand, G., Acta physiol. scand. 1946. *12*. 279.
Feldberg, W., Pflüg. Arch. ges. Physiol. 1933. *232*. 88.
Ferrier, D., Die Funktionen des Gehirnes. Braunschweig. 1879.
Fleisch, A., Z. Biol. 1929. *88*. 573.
Fleisch, A., Schweiz. med. Wschr. 1932. *39*. 873.
Fofanow, L. L., and Tschalussow, M. A., Pflüg. Arch. ges. Physiol. 1913. *151*. 543.
Folkow, B., Acta physiol. scand. 1952. *25*. 49.
Folkow, B., and Euler, U. S. v., Circulation Res. 1954. *2*. 191.
Folkow, B., Frost, J., Haeger, K., and Uvnäs, B., Acta physiol. scand. 1949. *17*. 195.
Folkow, B., Frost, J., and Uvnäs, B., Acta physiol. scand. 1948. *15*. 412.
Folkow, B., and Gernandt, B. E., Amer. J. Physiol. 1952. *169*. 622.
Folkow, B., Haeger, K., and Uvnäs, B., Acta physiol. scand. 1948. *15*. 401.
Folkow, B., Ström, G., and Uvnäs, B., Acta physiol. scand. 1950. *21*. 145.
Folkow, B., and Uvnäs, B., Acta physiol. scand. 1948 a. *15*. 365.
Folkow, B., and Uvnäs, B., Acta physiol. scand. 1948 b. *15*. 389.
Folkow, B., and Uvnäs, B., Acta physiol. scand. 1949. *17*. 191.
Folkow, B., and Uvnäs, B., Acta physiol. scand. 1950. *20*. 329.
Friedberg, C. K., Z. Neurol. 1931. *134*. 50.
Frumin, M. J., Ngai, S. H., and Wang, S. C., Amer. J. Physiol. 1953. *173*. 428.
Fulton, J. F., Liddell, E. G. T., and McKrioch, D., J. Pharmacol. 1930. *40*. 423.
Gaskell, W. H., The involuntary nervous system. London. 1916.
Geohegan, W. A., Wolf, G. A. Jr., Aidar, O. J., Hare, K., and Hinsey, J. C., Amer. J. Physiol. 1942. *135*. 324.
Gernandt, B., and Zotterman, Y., Acta physiol. scand. 1946. *11*. 301.
Gilding, H. P., J. Physiol. 1932. *74*. 34.

GLASER, W., Die Innervation der Blutgefässe. MÜLLER: Lebensnerven und Lebenstriebe. Berlin. 1931. p. 364.
GRANIT, R., and REXED, B., Nord. Med. 1942. *16*. 2899.
GREEN, H. D., and HARTZELL, H., Amer. J. Physiol. 1938. *123*. 81.
GREEN, H. D., and HOFF, E. C., Amer. J. Physiol. 1937. *118*. 641.
GUGGISBERG, H., Mutterkorn. Vom Gift zum Heilstoff. Basel. 1954.
HARE, K., and GEOHEGAN, W. A., Amer. J. Physiol. 1939. *126*. 524 P.
HARE, K., and GEOHEGAN, W. A., J. Neurophysiol. 1941. *4*. 266.
HARRISON, F., Arch. Neurol. Psychiat. Chicago. 1938. *40*. 563.
HARRISON, F., WANG, S. C., and BERRY, C., Amer. J. Physiol. 1939. *125*. 449.
HARTMAN, F. A., BLATZ, W. E., and KILBORN, L. G., J. Physiol. 1919. *53*. 92.
HERRICK, J. F., GRINDLAY, J. H., BALDES, E. I., and MANN, F. C., Amer J. Physiol. 1940. *128*. 338.
HESS, W. R., Die Methodik der lokalisierten Reizung und Ausschaltung subkortikaler Hirnabschnitte. Leipzig. 1932.
HESS, W. R., Das Zwischenhirn und die Regulation von Kreislauf und Atmung. Leipzig. 1938.
HESS, W. R., Helv. physiol. acta. 1947. *7*. Suppl. 4.
HESS, W. R., Die funktionelle Organisation des vegetativen Nervensystems. Basel. 1948.
HEYMANS, C., BOUCKAERT, J. J., FARBER, S., and HSU, F. Y., Amer. J. Physiol. 1936. *117*. 619.
HILLARP, N.-Å., and HÖKFELT, B., Acta physiol. scand. 1953. *30*. 55.
HILTON, S. M., J. Physiol. 1952. *117*. 48 P.
HILTON, S. M., and LYWOOD, D. W., J. Physiol. 1954. *123*. 64 P.
HOFF, E. C., Confinia Neurologica. 1949. *9*. 166.
HOFF, E. C., and GREEN, H. D., Amer. J. Physiol. 1936. *117*. 411.
HOLMGREN, A., Personal communication. 1955.
HOLTZ, P., ENGELHARDT, A., GREEFF, K., and SCHÜMANN, H. J., Arch. exp. Path. Pharmak. 1952. *215*. 58.
HORSLEY, V., and CLARKE, R. H., Brain. 1908. *31*. 45.
HOUSSAY, B. A., and MOLINELLI, E. A., C. R. Soc. Biol., Paris. 1925. *93*. 1454.
HUBER, G. C., CROSBY, E. C., WOODBURNE, R. T., GILLILAN, L. A., BROWN, J. O., and TAMTHAI, B., J. comp. Neurol. 1943. *78*. 129.
HUNSICKER, W. C. Jr., and SPIEGEL, E. A., Proc. Soc. exp. Biol., N. Y. 1934. *31*. 974.
JASPER, H. H., and AJMONE-MARSAN, C., A stereotaxic atlas of the diencephalon of the cat. Ottawa. 1954.
KABAT, H., MAGOUN, H. W., and RANSON, S. W., Arch. Neurol. Psychiat. Chicago. 1935. *34*. 931.
KAINDL, F., and EULER, U. S. v., Amer. J. Physiol. 1951. *166*. 284.
KARPLUS, J. P., Bumke u. Foersters Handb. Neurol. 1937. *2*. 402.
KARPLUS, J. P., and KREIDL, A., Pflüg. Arch. ges. Physiol. 1909. *129*. 138.
KARPLUS, J. P., and KREIDL, A., Pflüg. Arch. ges. Physiol. 1910. *135*. 401.
KARPLUS, J. P., and KREIDL, A., Pflüg. Arch. ges. Physiol. 1911. *143*. 109.

KARPLUS, J. P., and KREIDL, A., Pflüg. Arch. ges. Physiol. 1918. *171.* 192.
KARPLUS, J. P., and KREIDL, A., Pflüg. Arch. ges. Physiol. 1924. *203.* 533.
KARPLUS, J. P., and KREIDL, A., Pflüg. Arch. ges. Physiol. 1927 a. *215.* 443.
KARPLUS, J. P., and KREIDL, A., Pflüg. Arch. ges. Physiol. 1927 b. *215.* 667.
KARPLUS, J. P., and KREIDL, A., Pflüg. Arch. ges. Physiol. 1928. *219.* 613.
KELLER, A. D., Amer. J. Physiol. 1932. *100.* 576.
KNOLL, Ph., Beitr. Anat. Physiol. 1869. *4.* 109.
KROGH, A., and LINDHARD, J., J. Physiol. 1913. *47.* 112.
KUNTZ, A., The autonomic nervous system. Philadelphia. 1953.
LANGFORD, H. G., BERNHAUT, M., and HOFF, E. C., Proc. Soc. exp. Biol., N. Y. 1954. *87.* 561.
LANGLEY, J. N., J. Physiol. 1924. *59.* 231.
LANGWORTHY, O. R., and RICHTER, C. P., Brain. 1930. *53.* 178.
LARGY, C. DE, GREENFIELD, A. D. M., MCCORRY, R. L., and WHELAN, R. F., Clin. Sci. 1950. *9.* 71.
LIM, R. K. S., J. Physiol. U. S. S. R. 1938. *24.* 235.
LIM, R. K. S., WANG, S. C., and YI, C. L., Chin. J. Physiol. 1938. *13.* 61.
LINDGREN, P., Acta physiol. scand. 1954. *31.* Suppl. 114. 37.
LINDGREN, P., ROSÉN, A., STRANDBERG, P., and UVNÄS, B., J. comp. Neurol. 1955. To be published.
LINDGREN, P., and UVNÄS, B., Acta physiol. scand. 1953 a. *29.* 137.
LINDGREN, P., and UVNÄS, B., Circulation Research. 1953 b. *1.* 479.
LINDGREN, P., and UVNÄS, B., Amer. J. Physiol. 1954 a. *176.* 68.
LINDGREN, P., and UVNÄS, B., Acta physiol. scand. 1954 b. *32.* 259.
LINDGREN, P., and UVNÄS, B., Acta physiol. scand. 1955. *33.* 108.
LINDGREN, P., and UVNÄS, B., Unpublished observations.
LUDWIG, C., and THIRY, L., Sitz. Ber. Wien. Akad. Wiss. (Math.-Naturw. Kl.) 1864. *49, 2.* 421.
LUND, A., Cortex cerebris betydning for extremiteternes vasomotorik. Copenhagen. 1943.
LUND, A., Acta psychiat., Kbh. 1945. *20.* 213.
LUND, A., Acta psychiat., Kbh. 1947. *22.* 41.
MAGOUN, H. W., Amer. J. Physiol. 1938. *122.* 530.
MAGOUN, H. W., Res. Publ. Ass. nerv. ment. Dis. 1940. *20.* 270.
MAGOUN, H. W., RANSON, S. W., and HETHERINGTON, A., Amer. J. Physiol. 1937. *119.* 615.
MAGOUN, H. W., RANSON, S. W., and HETHERINGTON, A., Arch. Neurol. Psychiat. Chicago. 1938. *39.* 1127
MARBURG, O., and WARNER, F. J., J. nerv. ment. Dis. 1947. *106.* 415.
MATHISON, G. C., J. Physiol. 1910. *41.* 416.
MCDOWALL, R. J. S., The control of the circulation of the blood. London. 1938.
MCDOWALL, R. J. S., J. Physiol. 1950. *111.* 1.
MCQUEEN, J. D., BROWNE, K. M., and WALKER, A. E., Neurology. 1954. *4.* 1.
MONNIER, M., Rev. Neurol. 1938 a. *69.* 273.
MONNIER, M., Rev. Neurol. 1938 b. *70.* 521.

MONNIER, M., Arch. int. Physiol. 1939. *49*. 455.
MONNIER, M., Helv. physiol. acta. 1943. *1*. 437.
MÜLLER, L. R., Lebensnerven und Lebenstriebe. Berlin. 1931.
MÜLLER, L. R., and GLASER, W., Dtsch. Z. Nervenheilk. 1913. *46*. 325.
OTT, I., Quoted from BECHTEREW: Die Funktionen der Nervencentra. 1909.
OWSJANNIKOW, PH., Ber. Verh. sächs. Ges. Wiss. (Math.-Phys. Kl.), 1871. *23*. 135.
PITTS, R. F., and BRONK, D. W., Amer. J. Physiol. 1942. *135*. 504.
PITTS, R. F., LARRABEE, M. G., and BRONK, D. W., Amer. J. Physiol. 1941. *134*. 359.
PRUS, J., Wien. klin. Wschr. 1899. *12*. 1124.
RANSON, S. W., Psychiat. Neurol. Bl. (Festb. c. v. Ariens Kappers), 1934. *38*. 534.
RANSON, S. W., Res. Publ. Ass. nerv. ment. Dis. 1940. *20*. 342.
RANSON, S. W., and BILLINGSLEY, P. R., Amer. J. Physiol. 1916. *41*. 85.
RANSON, S. W., and MAGOUN, H. W., Ergebn. Physiol. 1939. *41*. 56.
RANSON, S. W., and WIGHTMAN, W. D., Amer. J. Physiol. 1922. *62*. 392.
RAPELA, C. E., and HOUSSAY, B. A., Rev. Soc. argent. Biol. 1952. *28*. 7.
RASMUSSEN, A. T., J. comp. Neurol. 1936. *63*. 501.
REDGATE, E. S., and GELLHORN, E., Amer. J. Physiol. 1953. *174*. 475.
REIGHARD, J., and JENNINGS, H. S., Anatomy of the cat. New York. 1935.
ROSENBLUETH, A., and CANNON, W. B., Amer. J. Physiol. 1934. *108*. 599.
ROSENBLUETH, A., and CANNON, W. B., Amer. J. Physiol. 1935. *112*. 33.
ROTHLIN, E., Schweiz. med. Wschr. 1946. *76*. 1254.
ROTHLIN, E., Bull. schweiz. Akad. med. Wiss. 1947. *2*. 249.
SACHS, E., J. exp. Med. 1911. *14*. 408.
SCHIFF, J. M., Untersuchungen zur Physiologie des Nervensystems I. Frankfurt a. M. 1855.
SCOTT, J. M. D., J. Physiol. 1925. *59*. 443.
SCOTT, J. M. D., and ROBERTS, F., J. Physiol. 1924. *58*. 168.
SHERRINGTON, C. S., The integrative action of the nervous system. Newhaven Conn. 1906.
SNELL, E. S., CRANSTON, W. J., and GERBRANDY, J., Lancet. 1955. *268*. 693.
SPIEGEL, E. A., Die Zentren des autonomen Nervensystems. Berlin. 1928.
SPIEGEL, E. A., and HUNSICKER, W. C. JR., J. nerv. ment. Dis. 1936. *83*. 252.
SPIEGEL, E. A., KLETZKIN, M., and SZEKELY, E. G., J. Neuropath. 1954. *13*. 212.
STRICKER, M. S., Sitz. ber. Keiserl. Akad. Wiss. Wien. 1876. *74*. 173.
STRICKER, S., Med. Jahrbücher. 1886. *1*. 1.
STRÖM, G., Acta physiol. scand. 1950 a. *20*. Suppl. 70. 83.
STRÖM, G., Observationer rörande den centralnervösa regleringen av blodflödet genom huden. Lund. 1950 b.
SUH, T. H., WANG, C. H., and LIM, R. K. S., Chin. J. Physiol. 1936. *10*. 61.
THOMPSON, W. C., and BACH, L. M. N., J. Neurophysiol. 1950. *13*. 455.
TOURNADE, A., and MALMÉJAC, J., C. R. Soc. Biol., Paris. 1933. *112*. 679.

Uvnäs, B., Nord. Med. 1949. *42.* 1719.
Uvnäs, B., Physiol. Rev. 1954. *34.* 608.
Vulpian, A., Leçons sur l'appareil vasomoteur. Paris. 1875.
Walker, A. E., Res. Publ. Ass. nerv. ment. Dis. 1943. *23.* 63.
Wall, P. D., and Davis, G. D., J. Neurophysiol. 1951. *14.* 507.
Wang, S. C., and Ranson, S. W., J. comp. Neurol. 1939 a. *71.* 437.
Wang, S. C., and Ranson, S. W., J. comp. Neurol. 1939 b. *71.* 457.
Weber, E., Arch. Anat. Physiol., Lpz. Physiol. Abt. 1906. *30.* 495.
Weil, A., Arch. Neurol. Psychiat., Chicago. 1928. *20.* 392.
White, J. C., Smithwick, R. H., and Simeone, F. A., The autonomic nervous system. New York. 1952.
Winkler, C., and Potter, A., An anatomical guide to experimental researches on the cat's brain. Amsterdam. 1914.
Woodburne, R. T., Crosby, E. C., and McCotter, R. E., J. comp. Neurol. 1946. *85.* 67.
Woollard, H. H., Heart. 1926. *13.* 319.
Yi, C. L., Chin. J. Physiol. 1938. *13.* 411.

UPPSALA 1955
APPELBERGS BOKTRYCKERI AB